AN INTEGRATED PRACTICE OF MEDICINE

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A Complete General Practice of Medicine From Differential Diagnosis by Presenting Symptoms to Specific Management of the Patient

By HAROLD THOMAS HYMAN M D

1184 Illustrations 305 in Color
319 Differential Diagnostic Tables

W B SAUNDERS COMPANY
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TO

WILLIAM COGSWELL CLARKE M.D. 1872–1943

LEO KESSEL M.D. 1881–1932

CHARLES CHRISTIAN LIEB M.D.

Who taught my ears to hear, my eyes to see

AND TO MY WIFE

MARION ANDERSON HYMAN

Her husband praiseth her, saying
Many daughters have done virtuously
But thou excellest them all

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PREFACE

This Integrated Practice of Medicine is a complete text conceived and written to meet the requirements of the general practitioner Its four volumes and special index volume are arranged and coordinated to deal realistically with diagnostic and therapeutic problems of the individual patient Cardinal objectives include (1) complete delineation of the broad and diverse fields of general practice (2) arrangement of material in the chronologic sequence of everyday practice and (3) integration of the various subjects so that each discussion focuses consideration on the human patient as a *biologic unity*

Conventional textbooks on the practice of medicine are usually limited to the subject matter of internal medicine a discipline which constitutes only a fraction of the responsibilities of the general practitioner An Integrated Practice of Medicine ' as minutely detailed later (see *Table of Contents* page xix) supplements the material of internal medicine with authoritative text devoted to the clinical subjects of *Infection Tropical Medicine Allergy Metabolic Disorders Poisonings Toxicology Neoplastic Disease Cardiology Hematology Endocrinology Psychiatry Neurology, Ophthalmology Dentistry Dental Surgery Gastro enterology Proctology Otology Rhinolaryngology Urology Gynecology Obstetrics Pediatrics Orthopedics Dermatology Minor Surgery Anesthesiology Emergency Major Surgery Convalescence* and *Rehabilitation* It includes brief but complete and accurate surveys of the preclinical sciences of *Anatomy Physiology Pathology Bacteriology Serology Immunology* and *Physiological Chemistry* as well as meticulous details of the practical clinical disciplines of *Physical Diagnosis Laboratory Methods Clinical Pathology Pathologic Physiology Electrocardiography Dietetics Radiology Prognosis Pharmacology* and *Therapeutics*

Differential Diagnosis —In contrast to standard textbooks which consist of a series of unrelated essays on individual subjects An Integrated Practice of Medicine delineates its problem to the reader in the manner in which the patient presents his clinical ailments to the practitioner Until the significance of a presenting symptom or sign has been correctly interpreted the physician is in no position to conduct intelligent therapy or to hazard a prognosis To assist in his clinical research 319 *Tables of Differential Diagnosis by Presenting Symptoms and Signs* have been prepared In general each table is placed with that clinical condition with which the symptom or sign is most frequently associated For example the Differential Diagnosis of Headache appears with Migraine of Stiff Neck with Meningitis of Rales with Physical Examination of the Chest of Cardiac Murmurs with Endocarditis and of Pain in the Right Lower Quadrant with Acute Appendicitis

quate This work aims to accomplish the objective so well defined by the Report of the Commonwealth Fund

SCOPE OF "AN INTEGRATED PRACTICE OF MEDICINE"

This Integrated Practice of Medicine is a complete survey of the fields of general medical practice Each of its twenty five constituent sections is capable of functioning as an independent text yet the subject matter of each section is interwoven with the subject matter of every other section so that the system as a whole functions as a coordinated unity

The Sections —The sections group themselves in the following natural subdivisions:

Bodily Injuries and Bodily Responses to Injury
- General Reactions of Bodily Tissues
- Infection
- Allergy
- Neoplasms
- Disturbances of Metabolism
- Poisoning

Disturbances of the Systems of Communication and Coordination
- The Circulatory System
- The Blood and Blood Forming Organs
- The Organs of Internal Secretion
- The Nervous System including the Voluntary Nervous System Involuntary Nervous System and Psychiatry
- The Eye

Disturbances of End Organ Systems
- The Digestive System
- The Respiratory System
- The Urinary System
- The Male Reproductive System
- The Female Reproductive System
- Obstetrics
- Pediatrics
- The Skeletal and Locomotor Systems
- The Tegumentary System

The Technics of Medical Diagnosis and Therapy
- Physical Diagnosis
- Laboratory Methods
- Medical Therapeutics including Pharmacotherapy
- Surgical Therapeutics

Prognosis
- The Art of Prognosis

Each section actually constitutes a textbook devoted to a particular clinical specialty Most have been written by a general practitioner the

For immediate reference and to coordinate the vast material an *Index of Differential Diagnosis* appears in the Index Volume

Since differential diagnosis is of necessity a discipline for the running reader a huge mass of material had to be concentrated into authoritative and concise tables Each of the latter usually could be confined to two columns As a general rule *the left hand column* of each table consists of listings of the various possible causes for the production of the presenting symptom or sign *the right hand column* contains a telegraphic description of clinical manifestations and diagnostic features together with suggestions for further investigations leading to a definitive recognition of the specific disorder The use of the tables permits the practitioner after elicitation of positive findings to narrow diagnostic possibilities to a few subjects to which page references are conveniently inserted Then when the diagnosis has been defined further study of the material provides accurate guidance toward prognosis and a therapeutic program

Integration.—Integration of the text has been accomplished by the *Tables of Differential Diagnosis* just referred to by *cross references* which appear throughout the textual material and by the *context* which emphasizes in each separate presentation the broad systemic consequences of local disturbances as well as local manifestations of systemic disease Illustrative of these general principles the chancre of syphilis is regarded as a portal of entry for systemic infection and not as a mere venereal manifestation the eruption of secondary syphilis is regarded as a local manifestation of a systemic disorder and not as a problem in dermatology

The cross references in parentheses throughout the text may be visually disconcerting to some but their inclusion is justified by the physical effort that is spared the reader By means of them the location of source material may be identified without repeated and fatiguing recourse to the indexes

An Integrated Practice of Medicine and the General Practitioner.—This Integrated Practice of Medicine has been written by active practitioners for the guidance of their colleagues It attempts to deal with the problems *of the individual patient who consults his personal physician and who* entrusts the grave responsibilities of his health and his life to a particular *doctor of medicine The latter functions alone or in consultation with a* specialist his theater of operation may be the office the home of the patient or a room in a hospital figuratively and literally he is concerned with the patient and the family group from cradle to grave and nothing that concerns his patient is foreign to him

The need for an integrated practice of medicine must be keenly apparent to each practitioner who has sought guidance by means of the written word With increasing emphasis on specialization in medicine and on the more glamorous aspects of research the educational requirements of general medical practice have been neglected The *Report of the Commonwealth Fund* (194) states that no short cut to the integration of specialized knowledge into comprehensive medical care has yet been devised but until this problem is solved medicine—and therefore training for medicine—will be made

previously described (p vii) The discussion of any particular symptom or sign may be located rapidly by reference to the *Index of Differential Diagnosis* in the Index Volume

Illustrations —In so far as possible atlases of illustrations are introduced in each section before the chapters that deal with clinical disturbances For the most part the illustrations are those of living rather than autopsy material since the practitioner must become familiar with such visual phenomena as eruptions x rays electrocardiograms charts external morphologic lesions and changes in body fluids

Clinical Disturbances —The clinical disturbances of the organ systems are usually presented under the headings of Congenital Anomalies Mechanical Physical and Chemical Injuries Neoplasms Infections and Inflammations and Neurologic and Vascular Affections Iteration of these subdivisions aids in training the mind to think of clinical medicine in orderly logical channels

The Clinical Entity —Each individual clinical entity is discussed in its proper place in appropriate detail Rare and unimportant diseases are usually dismissed of necessity with a summary of highlights The more important and commoner derangements are presented in complete fashion The text is usually subdivided into headings for *Etiology* and *Pathogenesis Pathology Clinical Manifestations Laboratory Data Course and Complications Prognosis* and *Treatment*

Etiology and Pathogenesis —The etiology and pathogenesis of each clinical derangement are discussed in detail wherever facts are available Recognition of the cause of an abnormality and of the manner in which it produces its noxious effects facilitates an understanding of the clinical manifestations and aids in the preparation of an inclusive therapeutic regimen

Pathology —For the most part details of pathology are given in bare outline The practitioner is essentially interested in the *function* of organs and his best therapeutic efforts are inaugurated before morphologic change has occurred *Surgical pathology* greatly concerns the practitioner who is constantly confronted with the specter of malignancy The biopsy specimen if benign affords him a happy measure of relief if malignant it indicates the necessity for urgent therapy

Clinical Manifestations —In the description of clinical manifestations of disease emphasis is directed particularly to *asymptomatic* stages and to *early symptoms and signs* The physician who does a routine physical examination is recurrently amazed at the frequency with which he discovers cardiac murmurs hypertension pulmonary tuberculosis infected tonsils carious teeth serologic evidences of syphilis gastric hyperacidity or hypoacidity anemia gastrovisceroptosis renal and biliary calculi uterine fibroids ovarian cysts prostatic enlargement malposition of the uterus cervical lacerations glycosuria albuminuria indicanuria intestinal infestations and obstinate constipation—at a time when the patient has no conscious registration of difficulty

In the symptomatic phases of disease the practitioner is confronted

senior author and a specialist Associate Editor Particular emphasis has been laid on *local disturbances* which reflect the derangement of the body as a whole and to *systemic disturbances* which may result from local lesions Thus the subject matter of each section is presented as a unit and as a part of a greater whole

Review of Basic Sciences.—Consistent with the belief that sound medical practice requires mastery of the basic sciences most sections include *summaries* of preclinical disciplines *Reviews of anatomy and physiology* introduce the sections dealing with Circulation, Blood Internal Secretions Neurology Ophthalmology Digestion Respiration Urinary Diseases Male and Female Reproductive Systems and the Skeletal and Locomotor Disorders

Concise details of *pathology* are scattered throughout the text *Bacteriology Immunology* and *Serology* are discussed with Infection The material on *Laboratory Diagnosis* is essentially a textbook of Clinical Pathology *Medical Therapeutics* contains the greater part of a volume on Pharmacology

Pathologic Physiology.—In many sections pathologic physiology is included in the introductory chapter since the subject matter is inexorably linked with considerations of normal function For example the topic of Uremia appears in the opening chapter of the section on the Urinary System Disturbances of Menstruation Ovulation Fertility and Sexuality are found with preliminary considerations of the Female Reproductive System and Backward and Forward Failure are described in the introduction to Disturbances of the Circulation These inclusive prefatory discussions emphasize the paramount importance of *performance* as contrasted with *morphologic change*

Technics of Diagnosis and Treatment.—In each section specific methods of diagnosis and treatment are described or listed with page reference to Volume IV This has been done in the interest of the reader who wishes to become acquainted with or to review the individual technics and their interpretations

Important differences between *academic* and *private* practice are illustrated in the approaches to diagnosis and treatment Economic considerations limit the availability of complicated and expensive examinations for the practitioner who utilizes laboratory investigations in a reluctant and miserly fashion rather than with the lavishness that is observed at a university hospital Symptomatic and palliative treatment is accorded full and ingenious exploration since the patient demands relief of his distress whether or not the diagnosis can be definitely ascertained There is repeated emphasis of the principle of *treating the patient* rather than the disturbance of an isolated organ or tissue The specialist errs if he undertakes local therapy without the knowledge and cooperation of the practitioner the practitioner errs if he trespasses too boldly upon specialist province and again if he fails to integrate specialist procedures for colleague and patient

Differential Diagnosis.—The Tables of Differential Diagnosis have been

culosis may have appendicitis lobar pneumonia or acne vulgaris just as does the more normal individual

Treatment —The closing portion of each presentation is devoted to the *art* and *science* of therapeutics In the course of twenty years of teaching in Pharmacology and a longer period in the practice of medicine the senior author has developed a full appreciation of the paramount importance of a complete and ingenious program aimed at the relief cure or prevention of disease in all of its manifestations

Prophylactic treatment has much greater significance in private practice than in institutional medicine Preventive medicine is best practiced by the medical practitioner who administers prophylactic immunizations instructs his flock in the principles of physical and mental hygiene and guides them in practical exercises in the art of living

Specific therapy is the most satisfactory and dramatic of the therapeutic sciences It may be conducted by the administration of serums and chemo therapeutic or anti infective agents it may involve the removal of a diseased appendix or lavage of an infected antrum It may be accomplished by the practitioner without specialist assistance or it may require cooperation and technical execution by the specialist

Symptomatic therapy requires the ingenious exercise of the arts and sciences of medicine Lacking the incisive benefits of specific therapy it invokes a variegated armamentarium a large fund of patience and devotion and sufficient humility to abandon fruitless measures and inaugurate fresh endeavors

The *Technics of Therapy* are summarized or presented in detail in Volume IV In those instances in which specific therapy is utilized for a single purpose the details are transferred to the section devoted to the particular subject Thus the material on anti infective agents appears in the section on Infection the products of internal secretion are described in the section on Endocrinology and digitalis and quinidine are dealt with in the section on the Circulatory Diseases

Each therapeutic device is described in complete detail in some one place so that pharmacologic aspects therapeutic possibilities and toxicologic hazards may be fully explored Thereafter each individual recommendation is followed by a page reference to the main article Thus penicillin and streptomycin are described in the section on Infection when these powerful antibiotics are used in the treatment of pneumonia *gonorrhea syphilis* or any other of the bacterial diseases their use is merely outlined and the reader is referred by page number to the inclusive discussion

The authors have made a point of expressing *personal opinions concerning* the usefulness or uselessness of various methods of therapy Readers who maintain opposite opinions on controversial matters are urged to communicate their views to the senior author in care of the publishers The practitioner is entitled to more than a catalogue of recommended remedial agencies and technics One of the weaknesses of many textbooks of therapy is the uncritical publication of long lists of reputed beneficial procedures many of

most frequently with *herald manifestations* which differ strikingly from later evidences and from end stages as seen in institutional medicine The classical physical signs of lobar pneumonia as commonly taught and described refer to evidences of consolidation as seen after forty eight to seventy two hours of illness the practitioner sees lobar pneumonia shortly after the initial chill when physical signs may be completely lacking or when *at most there is some percussion dulness with an element of tympany* diminished breath sounds of slightly increased pitch and an occasional subcrepitant rale The textbook signs of an appendicitis are in reality those of the complicating peritoneal reaction the practitioner is challenged by the problem of appendicitis at a time when the outstanding features are localized pain and tenderness unaccompanied by rigidity fever or leukocytosis The practitioner sees measles when the child has hyperemia of nasopharynx and conjunctiva and Koplik spots these phenomena may precede by twenty four to thirty six hours the cutaneous eruption which has almost invariably appeared by the time that the patient is brought to a hospital The practitioner deals with syphilis in the primary stage before serologic tests are positive and before late changes are apparent in aorta pupils and the nervous system

A textbook which is to be of value to the practitioner must be one in which emphasis is placed upon the *beginnings of disease* rather than the pre autopsy stages

Laboratory Data—The modern practitioner owes it to himself and his patient to establish an early and definite diagnosis by laboratory aids Diagnostic guessing games cannot be tolerated when a clinical condition is recognizable through a laboratory procedure In order to bring the facilities of the laboratory to the practitioner s office and the patient s home particular efforts have been made to list the apparatus and solutions that are required for the performance of routine tests outline the steps by which procedures are performed and indicate the interpretations of results

Course and Complications—The course and complications of disease are described in detail The practitioner unlike the institutional physician lives his life with his patient he must be prepared to anticipate long term implications of clinical disturbances and explore future possibilities In conditions such as scarlet fever rheumatic fever and tuberculosis his responsibilities extend beyond the termination of the acute phases of the disease he projects psychic emotional social and economic consequences of the infectious process and prepares his patient for necessary adjustments

Definitive Diagnosis—The chapter material on diagnosis features clinical and laboratory methods by which the exact nature of the condition may be established after due consideration of the problems of differential diagnosis as previously described

In the chronic diseases such as tuberculosis and syphilis emphasis is placed on the fact that it is not sufficient merely to establish the presence of the infection it is also necessary to estimate the degree of activity and the relationship to presenting symptoms The patient with syphilis or tuber

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Treatment.—The closing portion of each presentation is devoted to the *art* and *science* of therapeutics In the course of twenty years of teaching in Pharmacology and a longer period in the practice of medicine the senior author has developed a full appreciation of the paramount importance of a complete and ingenious program aimed at the relief cure or prevention of disease *in all of its manifestations*

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these have only the virtue of custom having been laboriously copied from one text to another merely for the sake of completeness

Dangers and *accidents* during therapy are emphasized since the practitioner is much more vulnerable to criticism than the institutional physician in the event that the therapeutic device results in the production of toxicity or death The limitations of the general practitioner are recognized and reference to the specialist is indicated for highly technical forms of treatment All technical procedures are briefly outlined however so that the practitioner may be equipped to enter into discussions with his consultant and then describe and evaluate the projected procedures for the patient and his family circle

Prognosis—The importance of prognosis and a general discussion of its art constitute the material for a separate Section (p 4093) In this chapter, emphasis is directed to the prime importance of prognosis to the patient whose greatest concerns are his chances for recovery the span of anticipated incapacitation and the amount of permanent disability that may be produced

Summary—Whatever may be the auspices of the meeting of doctor and patient it should be the aim of the practitioner to be a complete physician In conducting the management of his patient the modern physician recognizes the magnitude and complexity of the integrating mechanisms of the human body

Specialization has disadvantages Too often the specialist finds himself dealing with a condition rather than a patient He treats a case of ulcer or he does a hernia He may have little knowledge and less interest in the remaining cells that go to make up the human being He and his patient alike may suffer from his myopia and both may profit by the homely guidance of the practitioner

A comprehensive understanding of the problems of clinical medicine requires consideration of the unique character of the individual patient of the nature of the disturbance with which he is afflicted and of the host reaction to that derangement Successful medical practice is dependent upon the degree to which the course of the derangement may be modified by the knowledge and the skill of the physician by the exactitude with which diagnosis has been established and by the arts and sciences incorporated into the therapeutic program

An Integrated Practice of Medicine aims to correlate the clinical aspects of the practice of medicine for medical student interne younger practitioners of medicine physicians who have been diverted from civilian to military practice and for those who have spent their lives caring for home communities Younger men may be prepared for the tasks that lie ahead and the neophyte should be aided in the establishment of his office Older practitioners inundated by routine duties and the welter of special journals and monographs may obtain a single source for synthesis of the present material of everyday practice It is the hope of the authors that they have married the science of practice and the art of medicine and that

tangible data obtained from basic sciences have been thoroughly fused with the broader psychologic economic sociologic and humanitarian aspects of the doctor patient relationship

If An Integrated Practice of Medicine fulfils the requirements for which it has been devised it should be possible for the practitioner after taking the history and performing the physical examination to turn to the Index of Differential Diagnosis obtain a reference to the needed Tables of Differential Diagnosis establish a definitive diagnosis or be guided to additional examinations and tests by which the diagnosis can be established and then prepare a therapeutic routine to include symptomatic specific and prophylactic therapy for the relief or cure of the abnormal manifestation concerning which his patient has consulted him

HAROLD THOMAS HYMAN

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ACKNOWLEDGMENTS

The inadequacy of the printed word is nowhere more evident than in the expression of appreciation to those who have been of such inestimable assistance in the preparation of An Integrated Practice of Medicine Preceding many of the sections the names of the Associate Editors appear Most of these men have been in the Armed Services during the War many sent in preliminary material and never had the opportunity of seeing the finished product until type was set In each instance these colleagues have submerged their individual contributions and personalities to permit a unified presentation of the subject matter Such merit as is inherent in the section material rightly may be adjudicated to the credit of these Associates debit entries are distinctly the responsibility of the Senior Editor

Additional acknowledgments are due to the undernoted colleagues for their unselfish aid in assisting with the indicated Sections In the instance of Dr Elias Strauss his modesty and insistence on mere citation in the Acknowledgment prevented the Senior Author from including him as Associate Editor of the Sections dealing with Infection and Respiration

Elias Strauss M.D	*Infection and Respiratory System*
Lawrence S Kubie M.D	*Psychiatry*
Leo Davidoff M.D	*Neurology*
Robert A Lambert M.D*	*Ophthalmology*
Nicholas Ransohoff M.D	*Skeletal and Locomotor System*
Henry W Cave M.D	*Major Surgery*
Rose I Spiegel M.D	*Digestive System*

* Deceased

Finally it is a pleasure to do homage to the members of the publishing staff Only the traditions of W B Saunders Company prevent individual listing of those who have labored so loyally and efficiently in their efforts to initiate an amateur into the fine arts of bibliogony

Harold Thomas Hyman

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SECTION I

GENERAL REACTIONS OF BODILY TISSUES

CHAPTER 1

GENERAL REACTIONS OF BODILY TISSUES

THE tissues of the body are of a strikingly similar pattern The biological unit is the cell set in its stroma Each unit through complex and diverse systems of communication integrates and equilibrates with adjacent or distant structures and with the body as a whole

THE CELLS

Each organ or tissue possesses its unique and specific *cellular parenchyma* The cells may be fixed as in the kidney or liver The erythrocytes are actively circulating and wandering cells are capable of ameboid movement

With the exception of the mature erythrocyte the cells contain a *nucleus* usually separated by a nuclear membrane from the remaining *cytoplasm* The cytoplasm possesses *centrosomes* and *mitochondria* involved in cell division a *reticular* (Golgi) *apparatus* and *plasmosomes* concerned with nutritive materials and the products of cellular metabolism The envelope of the cell is its *cellular membrane* which is a semipermeable structure

CONNECTIVE TISSUES

The parenchyma of most tissues is set in a framework of connective or interstitial substance This forms a *matrix* which supports the individual cells or cell groups and the radicles of the vascular and nervous

systems The *stroma* may be loose and flexible, as in subcutaneous tissue or rigidly constructed as in cartilage or bone

THE SYSTEMS OF COMMUNICATION AND INTEGRATION

The Nervous System—The cells and tissues of the body are integrated by the nervous mechanism which wires the organism through anatomically demonstrable connections

Nerve impulses are initiated in a variety of ways They may be started as a response to a *peripheral stimulus* Movement may occur voluntarily An *emotion* may be reflected through the entire involuntary nervous system best illustrated by the visible mechanisms of blushing and blanching The respiratory center in the medulla responds delicately to *chemical influences* such as anoxemia or excess of carbon dioxide in the circulating blood Peripherally the cholinergic system is stimulated by the local presence of *acetylcholine which is inactivated by a tissue enzyme cholinesterase* A peripheral nerve may be stimulated *mechanically* or by an *electrical current*

The nervous system as a whole is divisible anatomically physiologically and especially pharmacodynamically into the voluntary and involuntary components The *voluntary system* possesses a remarkably expanded cerebrum the midbrain a spinal cord with its pathways afferent and efferent peripheral nerves and nerve endings The afferent or sensory portion is the receiving mechanism recording occurrences at the periphery *The efferent or motor mechanism is mainly* concerned *with the tonus and* contractility of the striated muscles

The more primitive *involuntary nervous system* operates below the level of consciousness and functions beyond the province of the will It is influenced in varying degree by the emotions through a supramedullary connection that probably exists in the region of the thalamus Its automatic activities are controlled and regulated in the vital medullary centers Peripherally the involuntary nervous system is made up of two reciprocal and mutually antagonistic portions The *cholinergic* (craniosacral vagal *or parasympathetic) system is best characterized by its ability to be stimulated* by acetylcholine and depressed or paralyzed by atropine The *adrenergic* (thoracicolumbar or true sympathetic) system exhibits a characteristic stimulant reaction when exposed to effective doses of epinephrine The involuntary nervous system through cholinergic and adrenergic branches innervates all visceral structures the arteries and veins the glandular mechanisms and the vast vasodermal apparatus

Humoral Systems—Besides the neurogenic mechanism the body is coordinated through changes in the circulating fluid The blood which flows *in the vascular channels alters and is altered by each individual* cell with which it comes in contact The humoral control is dependent upon the integrity of the vascular tree and its contents

The *vascular system* consists of arteries capillaries and veins lymphatic channels sinuses and nodes The distributing arteries ramify into arterioles which terminate in the capillaries The vast capillary bed is lined by a single endothelial layer whose permeability approaches that of the cell membrane The fluid content of the capillary bed altered by interchange with the parenchymal structures flows into the terminal venules

of the collecting system thence by the larger venous radicles to return to the cardiac chambers for recirculation Lymphatic channels follow the course of the venous collecting system Their course is interrupted in places by dilated sinuses and the interpolation of the system of lymph nodes which act as depots

The *circulating fluids* of the body consist of blood lymph and tissue juices The latter two are similar in composition and contain the waste products of metabolic activity Endogenous bodily integration for the most part is accomplished by the circulating blood This remarkable fluid is made up of cellular elements and a clear plasma Whole blood volume approximates 10 per cent and plasma 5 per cent of body weight The average man weighing 150 pounds has 6300 cc of circulating blood Its pH varies between 7.3 and 7.45 and its cytology is represented by erythrocytes leukocytes and thrombocytes

The chief recognizable *chemical constituents of the blood* (Table 1) include albumin globulin fibrinogen the amino acids urea uric acid ammonia creatine creatinine the lipids cholesterol the cholesterol esters glucose iron sodium potassium calcium phosphorus chloride magnesium iodine and copper Oxygen and carbon dioxide exist in loose combination in the blood In addition to chemically identified substances blood contains the products of the internal secretory glands antibodies vitamins and various enzymes and anti enzymes

TABLE 1 —THE CHEMICAL COMPOSITION OF NORMAL SERUM PLASMA AND WHOLE BLOOD
(Values expressed in mg per 100 cc unless otherwise stated)

Serum	
Bilirubin	0.25–0.8
Calcium	9–11
Carbon Dioxide Combining Power	50–60 vol per cent
Chloride	350–390
Icterus Index	4–6
Magnesium	2–3
Phosphatase	
Alkaline	5 Bodansky units 14 King and Armstrong units
Acid	0–1.1 S.J.R. units
Phosphorus	3–4
Potassium	16– 2
Protein (gm per 100 cc)	
Total	6.5–8.0
Albumin	4–6
Globulin	1.5–2.5
Albumin Globulin Ratio	2 1
Sodium	315–330
Water	91–92 per cent

Plasma	
Carbon Dioxide Combining Power	0–60 vol per cent
Chloride	570–6 0
Cholesterol	160– 00
Cholesterol Ester	110–145
Fibrinogen	300–600
Whole Blood	
Amino Acid	5 8
Creatine	1–2
Glucose	80–120
Hemoglobin	13–17 gm
Iron	46–55
Nonprotein Nitrogen	25–35
Oxygen Capacity	18–21 cc
Sulfates	3–5
Urea Nitrogen	10–15
Uric Acid	2–4

BLOOD AND CELLULAR INTERCHANGE

The interchange between the blood and the cells is effected through the thicknesses of at least two semipermeable membranes that of the

lining endothelium of the capillaries and the cellular envelope of each basic biological unit The interchange of materials is determined by *hydrostatic* and *osmotic pressure* relationships as well as direct activity on the part of the cells In general these forces regulate cellular ingress of water and needed nutriment and the egress of waste and secretory products essential to the economy of the body as a whole (p 703)

INTEGRATIONS AND EQUILIBRATIONS

Each tissue carries on its intrinsic function or functions modified by *humoral changes* produced through the circulating fluid and *nervous factors* relayed through the integrated neurogenic mechanism

Each local process adds to or modifies the sum of the reactions of the body as a whole through alterations in the fluid contents of the returning vascular systems and through nervous influences by way of afferents Local and systemic equilibriums are maintained through altered osmotic relationships between cells and circulating fluids and by the interplay of the antagonistic innervations particularly in the realm of the involuntary nervous system

FUNCTION AND FORM

Medical thinking in the *Era of Morphology* held to the relationship between function and form Morphologists and histologists believed that the performance of an organ or a tissue could be estimated by the gross or microscopic appearance

The growth of physiology and biochemistry and the birth of the *Era of Function* have tended to widen the scope of clinical medicine beyond the limited concept of the organicist It is true that valuable inferences concerning function may be suggested after observation of morphological changes Nevertheless profound functional change occurs without anatomical or histological equivalents Indeed in certain instances as in hyperplasia of the thyroid gland identical histological appearances may be associated with alleged hyperfunction as in hyperthyroidism and diminution or absence of function as in cretinism (p 1191)

ALTERATIONS IN CELLULAR LIFE

The life of the individual cell follows the pattern of the life of the individual human being The cell is produced by its like There is a period of growth followed by a relatively stationary era of maturity This in turn gives way to a phase of decline and death followed by rebirth in the surviving organism

Life Span—The duration of life differs with the different cells The erythrocytes which can be accurately followed enjoy a life span of from 25 to 50 days though survival may last as long as 100 days The less differentiated cells such as those of the connective tissue stroma are probably hardier and longer lived

Anabolism (Growth)—Each cell has an anabolic phase or period of normal growth Modifications of growth include hypertrophy hyperplasia hypoplasia atrophy and dysplasia

Hypertrophy and Hyperplasia—Abnormal enlargement of tissue is described as *hypertrophy* an increase in the bulk of tissue as the result of a greater number of cells is *hyperplasia* Hypertrophy and hyperplasia may

occur concurrently Neither hypertrophy nor hyperplasia however need necessarily be associated with hyperfunction (Fig 1)

Hypertrophy and hyperplasia may be induced by a variety of factors A *work hypertrophy* is effected by effort as in the muscles of the athlete or the manual laborer *Compensatory hypertrophy* is observed in a remnant of an organ when significant portions have been destroyed or surgically removed Hyperplasia also results from *chemical influences* A decrease in iodine *storage causes* hyperplasia *of the thyroid gland* Mammary and genital hyperplasia are dependent upon *endocrine influences*

Hypoplasia and Atrophy—Diminished and impaired cell growth lead to hypoplasia and atrophy These abnormalities may be inherent in the cell (*congenital*) they may result from *endocrine disturbances* (cretinism pituitary dwarfism) *they* also follow impoverishment of blood supply (*ischemia*) or interruption of innervation (*postneuritic atrophy*) (Fig 1)

Dysplasia and Malignancy—Disorders of growth in which the pattern of development has been disturbed *are* termed dysplasias Dysplasias may be characterized by wild and undisciplined growth with invasive and metastatic characteristics as seen in the malignancies (p 572)

Degeneration—As the result of injury individual cells exhibit degenerative changes Dependent upon the character of the alteration pathologists recognize parenchymatous degeneration hyaline *metamorphosis* amyloidosis fatty glycogen and pigmentary degenerations and depositions of calcium or uric acid

Parenchymatous Degeneration—*Cloudy* swelling or parenchymatous degeneration usually occurs as a temporary phase during the course of an acute infection or an intoxication The tissue has the appearance of having been boiled The nature of the swelling of the cells is not clear Cloudy swelling of the kidneys is easily recognized by the appearance of albuminuria *From* the clinical standpoint it is most important to appreciate that *the injury is not irrevocable* Complete recovery usually occurs when the provocative agency ceases to operate (Fig 1)

Hyaline Metamorphosis—Hyaline metamorphosis results when translucent deposits of epithelial *or* connective tissue origin occur in tissue *These may be seen in the striated muscle during typhoid fever in thrombi* in uterine tumors and in the nephron in nephritis Death of tissue precedes conversion into hyaline Hence the prognosis *of* hyaline degeneration is less favorable than of simple cloudy swelling (Fig 1)

Amyloid Infiltration (*Amyloidosis*)—*The term* amyloidosis is misleading as it was *originally* believed that the condition was due to a deposition of a carbohydrate allied to starch It has since been found that the substance is a protein probably a combination of albumin and chondroitin sulfuric acid derived from *a long* continued destruction of organs rich in elastic connective tissue Amyloidosis is a very late complication of *chronic osteomyelitis suppurative arthritis pulmonary tuberculosis* or breaking down of a *gumma* (Fig 1)

The suspicion of amyloidosis arises when *hepatomegaly splenomegaly* and *persistent albuminuria* develop during chronic illness The diagnosis of clinical amyloidosis depends upon the reaction to the injection of Congo red Under normal circumstances the injected dye is retained in the blood and is recovered in appreciable amounts at the end of one and two hours

lining endothelium of the capillaries and the cellular envelope of each basic biological unit The interchange of materials is determined by *hydro static* and *osmotic pressure* relationships as well as direct activity on the part of the cells In general these forces regulate cellular ingress of water and needed nutriment and the egress of waste and secretory products essential to the economy of the body as a whole (p 703)

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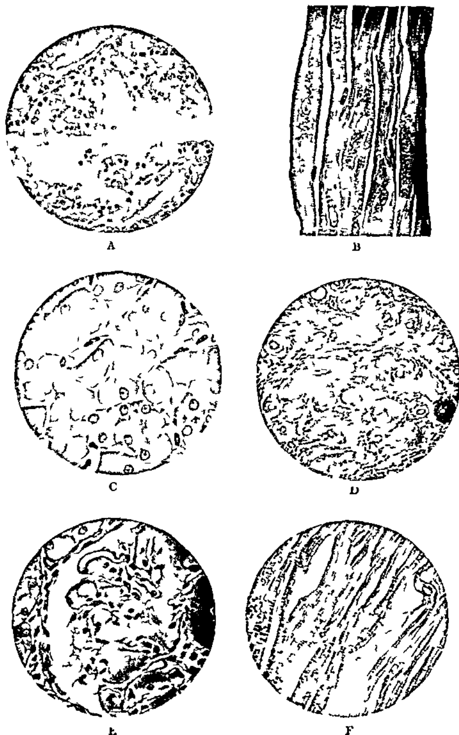


Fig 1 — Alterations in cellular pathology (MacCallum) *A* Hypertrophy and hyperplasia of the thyroid gland *B* Brown atrophy of the heart *C* Parenchymatous degeneration ("cloudy swelling") *D* Hyaline vessel walls in uterine tumor *E* Amyloid in glomerulus *F* Fatty heart muscle

In amyloidosis the tissues absorb the dye so that over 60 per cent of the dye disappears from the blood stream and is held in the degenerated cells

Because of the efficiency of modern treatment amyloidosis has become exceedingly rare When present it is almost invariably *irreversible* and imposes *an ominous prognosis*

Fatty Degeneration—Fatty degeneration is encountered in liver cells nerve tissue heart and blood vessels It is caused by the action of toxins which may be bacterial or chemical (phosphorus or chloroform) or by anoxemia of the local tissues as occurs in pernicious anemia (Fig 1)

Fatty and lipoid degenerations have widespread implication *Atherosclerosis* is attributed to the deposition of a lipoid (cholesterol) as the result of inadequate excretion of ingested cholesterol The origin of gall stones is essentially related to the precipitation of cholesterol In the *nephrotic states* the urine contains doubly refractile lipoids and blood chemical examinations characteristically reveal a massive hypercholesteremia Fatty infiltrations characterize metabolic disturbances such as

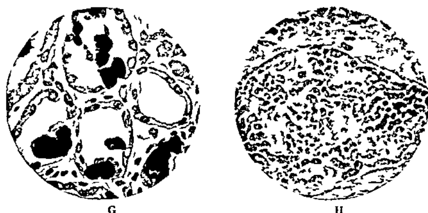


Fig 2—Alterations in cellular pathology (MacCallum) *G* Calcification of necrotic renal epithelium in mercury poisoning *H* Nodular cirrhosis of liver

hypothyroidism anemia and the whole series of the vaguely defined and poorly understood *lipoidal diseases* (p 1133)

Glycogen Infiltration—Glycogen infiltration appears in tissues that show a pathologic decrease of fat It is abundant in some tumors especially *hypernephromas* (p 2326)

Pigmentary Degeneration—Pigmentary degeneration may be due to the deposition of melanin lipochromes or derivatives of hemoglobin Pigment is normally present in skin hair and eyes but is excessive in adrenal cortical insufficiency (*Addison s disease*) Lipochromes or colored fats are the result of prolonged degeneration of cytoplasm as occurs in *brown atrophy of the heart* complicating untreated pernicious anemia or in *senile degeneration of nerve tissue* Blood destruction causes deposition of fractions of hemoglobin *Bronze diabetes* or *hemochromatosis* is a pigmentation disorder presumably resulting from disturbances of iron metabolism (p 606)

Mineral Deposits—Mineral deposits occur as part of degenerative

derangements *Calcification* is a prominent feature of the necrosis of the renal tubules in *mercury poisoning* and of the vascular lesion of *arterio sclerosis* Pathologic calcification occurs when the blood is flooded with calcium as after overdosage with parathyroid extract in certain of the decalcifying diseases and following ingestion of large amounts of vitamin D Necrotic areas in chronic infections such as empyema or pericarditis undergo calcification

The deposition of *uric acid crystals* in the tissues is an integral mani festation of the clinical disturbance of *gout* (p 2867)

Catabolism—Cellular atrophy and death complete the cycle of the individual cell The catabolic processes may terminate in *desiccation* and *simple atrophy* Premature death or the effects of a lethal injury result in a degenerative infiltration with liquefaction and autolysis manifested by *necrosis* and *gangrene*

Cellular Regeneration (Recovery)—The miracles of rebirth and reincar nation go on in countless cells every second of the life of the individual In *the surviving organism death of cells may be followed by cellular replace* ment and/or connective tissue change with or without compensatory hyperplasia The regeneration of parenchyma varies tremendously with different tissues The liver cell and surface epithelium show the most com plete powers of restitution whereas nerve tissue has the poorest

Connective Tissue Replacement (Scarring)—Under abnormal circum stances cellular death may be followed by connective tissue replacement This constitutes *sclerosis cirrhosis* or *fibrosis* the various terms meaning one and the same thing (Fig 2)

With connective tissue replacement of the parenchymal cells the gar den as it were goes to weed Unless the remaining integers undergo compensatory hypertrophy or hyperplasia function suffers in direct pro portion to the number of displaced cellular elements Failing this repara tive mechanism function may be vicariously assumed by some other tissues as is seen particularly in erythrogenesis

Compensatory Hyperplasia and Vicarious Functioning—The organicist mournfully surveys the connective tissue replacement under the micro scope utters solemn and ominous forebodings and despairs of therapeutic endeavor But it is the compensatory and vicariously assumed mechanisms that so delight the practitioner favoring his optimistic attitudes and prognoses

Immortality—In the end it is only the gonadal cells that survive Our ancestors live in us We in unbroken line achieve immortality in our progeny For the commoner cells 'the paths of glory lead but to the grave What transpires with them from that point on is more properly the province of the theologian

ALTERATIONS IN BODY AND TISSUE FLUIDS (HUMORAL CHANGES AND EFFECTS)

Oligemia Anemia and Ischemia—A decrease in the *amount* of blood is oligemia The *quality* is impaired in anemia (p 1055) A local *ischemia* is produced intravascularly by an embolism or a thrombosis extravascularly through pressure on a main arterial trunk or a vasomotor narrowing due to spasm

Effects of Ischemia (Infarction Necrosis and Gangrene) —The effects of the local ischemia are dependent upon the completeness and duration of the activating process and the ability to provide a collateral circulation With an effective *collateral circulation* the local ischemia produces little or no tissue damage In the absence of an effective collateral circulation an impoverishment that is complete and of long duration produces cellular death in the involved area The infarcted area may undergo necrosis and/or gangrene Should this occur in a loop of bowel or an extremity the life of the patient is spared by a timely resection or amputation

Dehydration and Desiccation —Dehydration and desiccation result from a negative water balance The body loses fluid through the several excretory channels Ordinarily the daily water output averages 150 cc through feces 1500 cc in urine 350 cc in expired air and 500 cc by way of the skin

Dehydration especially through the fixed loss by respiratory and tegumentary routes results from (1) deprivation of fluids (2) excessive loss through normal channels (vomiting diarrhea polyuria sweating) (3) abnormal fluid leaks due to hemorrhage and drainage of body fluids The more profound causes of dehydration relate to the tissue fluids and cells Relative changes in *osmotic* and *electrolytic* relationships produce cellular dehydration that may be associated with increase in blood volume Thus the injection of hypertonic saline and the ingestion of sea water by shipwrecked sailors result in a hyperchloridemia and increase of blood volume at the expense of cellular hydration (p 702)

The effects of dehydration are widespread and devastating They exceed in gravity tissue hunger and starvation The organism suffers loss of weight a disturbance in acid base balance toward the acid side a rise in nonprotein nitrogen of the blood thirst dryness of the skin and an aseptic pyrexia (p 23)

Plethora Hyperemia and Polycythemia —Prolonged increase in the amount of circulating fluid is *plethora* A true plethora occurs when the blood is increased without change in composition A *hydremic* or *serous* plethora is present when the fluid increase is essentially the result of an excess of the watery portion of the blood

An increase in the amount of blood to any given part is *hyperemia* Hyperemia may be active when there is an actual increase in the amount of arterial blood More often the practitioner encounters passive hyperemia when the outflow of venous blood is retarded (passive congestion) through local obstruction or heart failure

An increased number of erythrocytes per unit volume is *polycythemia* This occurs physiologically at higher altitudes Rarely it is a pathological condition of unknown causation and mechanism (p 1003)

Edema and Water Intoxication —Increase of the tissue fluid produces edema (p 706) Generalized edema is described as *anasarca* Localized edema of the peritoneal cavity is *ascites* of the pleural cavity *hydrothorax* of the pericardial cavity *hydropericardium* of the tunica vaginalis *hydrocele* and of a joint cavity *hydrarthrosis*

The causes for the development of edema may be local and/or generalized A *localized inflammatory or obstructive process* may give rise to an isolated outpouring of tissue fluid or lymph An increase in systemic

derangements *Calcification* is a prominent feature of the necrosis of the renal tubules in *mercury poisoning* and of the vascular lesion of *arterio sclerosis* Pathologic calcification occurs when the blood is flooded with calcium as after overdosage with parathyroid extract in certain of the decalcifying diseases and following ingestion of large amounts of vitamin D Necrotic areas in chronic infections such as empyema or pericarditis undergo calcification

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wholly a hydremic plethora due to increased water intake or decreased water output without alteration in osmosis electrolytic relationships or changes in the membrane Water intoxication may result in lowering of systemic temperature vomiting coma and convulsions (p 1519)

Intravascular Abnormalities (Thrombosis and Embolism)—One of the great protective mechanisms is the ability of the fluid blood to clot when it is removed from the vascular channels Intravascular clotting or thrombosis also occurs and may be reparative or pathological (p 1123)

A *reparative intravascular thrombosis* assists in the healing of a roughened or fractured endothelium and in the obliteration of a ligated vessel



Fig 4—Hemorrhagic infarct of lung (MacCallum)

Should the reparative thrombosis proceed to the point of occluding a vital artery as in coronary blockage the results may be an infarction of tissue with a serious if not fatal outcome A diffuse and generalized intravascular thrombosis occurs with certain of the rarer blood dyscrasias

Intravascular thrombosis in peripheral veins or the cardiac chambers possesses more than purely local hazards When fragments of the thrombus break off they are thrown as foreign bodies or *emboli* into the general circulation Embolization of a vital structure may produce sudden death If the initial shock is survived the outcome depends on the effectiveness of the collateral circulation With adequate compensation complete resti

venous pressure as in heart failure produces a generalized anasarca or a purely local collection of tissue fluid in dependent parts (pretibial)

The hydrostatic edemas as in heart failure are easier to understand than those involving altered osmotic relationships The latter depend for the most part on changes in the blood proteins and the electrolytes Thus a *hypoproteinemia* as in nephrosis produces edema through reduction in osmotic pressure of the depleted circulating fluid A salt edema on the



Fig 3—Thrombus in vena cava (MacCallum)

other hand results from an increase in the storage of electrolyte in the tissue fluids The edema of shock and inflammation most probably results from injury to endothelium perhaps by anoxia or by a histamine like substance Thus the derangement may involve the quality and composition of the circulating fluid the integrity of the filtering membranes the quality and composition of the tissue fluids or intracellular components

Water intoxication differs from edema in that the abnormality is

The practitioner who lives his life with his patients knows these individualities He anticipates the responses and deals with them the more effectively in the light of previous experience Astute patients recognize this It is to this that they refer when they state My doctor knows me inside and out

The initiation of the changes in the involuntary nervous system may be *physical chemical pharmacologic or psychogenic* This latter mechanism links emotional and cellular derangements producing the psychosomatic disturbances

Psychosomatic Affections.—Clinicians recognize that psychogenic disturbances may give rise to demonstrable and measurable alteration in the tissues The practitioner comments upon a constitutional nervous diathesis in peptic ulcer hyperthyroidism the dyspepsias mucous colitis the neurodermatitides the allergic and hypersensitive states essential hypertension the migraines and the epilepsies (p 1344)

Modern medicine has grouped these disturbances as psychosomatic These fascinating clinical syndromes are recognizable as end organ manifestations of a more or less profound derangement in the emotional or affective sphere They are essentially conversion or transference neuroses (p 1353)

Certain of the psychosomatic phenomena are demonstrable blushing and blanching illustrate *vasodilatation* and *angiospasm spastic viscera* are easily felt and readily seen in radiographic visualizations with barium *emotional tachycardia hypertension hyperglycemia* and *glycosuria* are measurable and obvious Many of the psychosomatic manifestations can not however be demonstrated These possess an element of mystery to the practitioner of skeptical mind Organicists have little patience with or understanding of these relationships They tend to dismiss the subject as fanciful and label the patient as a hypochondriac

The intermediate pathway between the psyche and the end organ is through the intervention of the involuntary nervous system Hence the management of the psychosomatic disorder concerns itself (1) with the *characterological* or *situational disturbance* (2) the manifestations of the derangement in the realm of the local end organ (*individual reaction picture*) and (3) the altered innervation through the involuntary nervous system (*autonomic imbalance*)

Psychosomatic manifestations are characterized by their increased incidence in the scale of civilization They are reproduced only with difficulty in lower animals They are seen relatively infrequently in those who live close to the earth and survive by the ardors of their physical labors They are seen most commonly in sedentary hypercivilized individuals They are truly the *Disturbances of Civilization*

TYPES OF BODILY INJURY

The human body is liable to many and diverse injuries The biologist and physician alike wonder at the resistance of the organism to trauma and at the viability of tissue The practitioner is recurrently amazed at the survival of a patient riddled for example with carcinomatosis Reduced to skin and bones such patients often function for days and even weeks without partaking of any nourishment and only minimal amounts of fluid

tution ensues Imperfect collaterals result in partial or complete infarction *Embolectomy* is a recent surgical advance which may be of great value in an accessible vessel such as an iliac artery

NEUROGENIC DISTURBANCES

The integrity of tissue is dependent upon humoral effects and the efficient operation of the neurogenic mechanisms

Disturbances of the Voluntary Nervous System—Injuries to the voluntary nervous system produce their tissue effects directly upon the local cellular structures Disuse and degeneration of nerves give rise to cellular atrophy and replacement by connective tissue (*atrophy of disuse post neuritic atrophy*)

The character of the clinical derangement depends on the site of the abnormality A disturbance affecting an afferent nerve produces *abnormalities of sensation* or *anesthesia* Efferent lesions are followed by *weakness* or *paralysis* The paralysis is flaccid if the nerve is severed or crushed peripherally spastic if the lesion is situated in the cord (spastic paraplegia) or centrally

Affective responses depend upon the *personality panel* of the individual These are familiar to the practitioner He recognizes the stoic and the patient who stands pain poorly the optimist and the pessimist the moody and the stable the weaklings and the strong in character This knowledge often influences diagnosis and is of great prognostic significance The practitioner regards with greater gravity the complaint of pretty bad pain when the patient is known to be hyposensitive He is less impressed by a report of 'agonizing excruciating anguish when it emanates from a chronic complainer with a low pain threshold Prognostically, the wise doctor knows well which of his patients can endure illness invalidism and discomfort He fears for those who have not the character or fortitude to face the trials that necessarily are part of the experience of each life

Disturbances of Involuntary Nervous System (Autonomic Imbalance)—Alterations in the involuntary nervous system effect local manifestations by changes in motor and secretory mechanisms They are best illustrated in the visible vasocutaneous structures Dilatation of the blood vessels as illustrated by blushing causes a local hyperemia Vasoconstriction and blanching produce a local anemia which if sufficiently prolonged may result in infarction and death

The Reaction Picture of Autonomic Imbalance—The variety in the clinical manifestations of vegetative disorders is confusing Attempts to codify the derangements as *vagotonia* and '*sympathicotonia* have added to the dilemma since pure forms of these disturbances are rarely if ever demonstrable It is of importance to recognize merely the realm of the abnormality and the concept of an 'autonomic imbalance (p 139)

The individual manifestation of the autonomic imbalance depends upon the end organ rather than the nerve trunk Each of us has a characteristic "*reaction picture* that is as individual and constant as our fingerprints Thus on emotional provocation one will blanch another blush this one develops diarrhea and that one nervous indigestion There is no manner in which the reaction picture may be predicted or explained but once observed it recurs with constancy no matter what the stimulus or cause

desis of the wandering cells particularly the leukocytes The outpouring of the tissue fluid and the wandering cells gives rise to swelling or *edema* which with *redness* and *heat* constitute the cardinal symptoms of inflammation

After a time the stream in the blood vessels appears to slow particularly in the venules The corpuscles seem to float in the center of the stream so that there is a clear layer of plasma between the column of erythrocytes and the vein wall Leukocytes appear in this marginal stream and adhere to the vein wall They assume the shape of a dumb bell and make their way through the endothelium and into the tissue of the inflammatory zone Along with the leukocytes a few red blood corpuscles escape passively into the area At this time the tissue fluid which is coagulable lays down a delicate network of *fibrin* By a positive chemotaxis the cells and the fluid approach the point of maximum injury

As the result of increased vascularity and excessive tissue fluid the part becomes tense and *pain* is produced Thus the local clinical mani

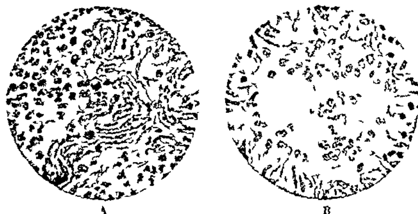


Fig 5—Types of inflammation (MacCallum) *A* Acute variety in lobar pneumonia *B* Chronic variety in pulmonary tuberculosis

festations of the acute inflammatory process are *redness heat swelling* and *pain* If the sum of the reactions is sufficient systemic evidences are manifest by measurable fever leukocytosis and the serological phenomena associated with immunity

The Sequels of Inflammation—With the advent of the leukocytes the forces of the inflammatory reaction are drawn for the conflict The process may terminate (1) in complete victory for the host with uneventful *recovery* (2) by suppuration and survival of the host at the expense of a local tissue loss (*laudable pus*) (3) by partial success and *fibrosis* (4) by a stalemate (*chronic inflammation*) and (5) by defeat of the host and his *death*

The practitioner and surgeon may intervene in the inflammatory struggle The former may prescribe local physiotherapy he may employ specific chemotherapeutic and biotherapeutic measures he strives to assist the tissue response and weaken or destroy the invader The surgeon applies similar ministrations in addition he drains pus and removes necrotic

Like the cacti of the desert they seem to thrive on the will to live defying the rules of metabolism

Physical Trauma—Body injuries may be physical as from *wounds* or external trauma they may be of *electrical* or *radioactive* origin

Chemical Injuries—Chemical injuries are exogenous or endogenous The former result from the ingestion of poisons Endogenous derangements include *acidosis anoxemia* and *uremia*

Obstructive Phenomena—Obstructive phenomena constitute an important and usually remediable type of clinical disturbance The hollow viscera the urinary or biliary passages may become blocked by pressure from without or by plugging from within (*calculi*) Vascular occlusions result from *embolism* or *thrombosis* (Figs 3 and 4 pp 12 and 13)

Infection—Perhaps one third to one half of all clinical disturbances follow invasion of the host by a living organism These phenomena constitute infection which is discussed in a separate section (p 37)

TYPES OF BODILY RESPONSE

The body responds to injury by various devices Some of these are usually favorable others appear to be harmful

The usually favorable bodily responses include *inflammation fever* (p 19) and *immunity* (p 73) The usually unfavorable body responses are *allergy* (p 547) and the development of *dysplasia* with invasiveness (p 572)

Inflammation—Inflammation is a complex phenomenon produced by the protective and defensive reaction to injury of the tissues and blood vessels The concept of inflammation is commonly limited to the visible morphologic alterations that occur A broader view would include the immunological phenomena demonstrable serologically but invisible histologically

The local inflammatory process if sufficiently extensive gives rise to a systemic and measurable *pyrexia* From the standpoint of the clinician the production of fever as measured by the clinical thermometer the inflammatory response seen by the pathologist the cytological changes encountered by the hematologist and the immunological mechanisms demonstrated by the bacteriologist and serologist are all manifestations of a single fundamental process

Types of Inflammation—The inflammatory process may be *acute subacute* or *chronic* It may terminate by *regeneration* and complete recovery by connective tissue replacement or *fibrosis* and scar formation by *suppuration* or the formation of pus or by *necrosis gangrene* and *death*

The Inflammatory Reaction Viewed Histologically—Inflammation is initiated by a *dilatation of the blood vessels* In all likelihood the increase in the vascular bed is produced by a paralysis of the capillaries resulting from a poisoning by some substance resembling or identical with *histamine* derived from injured tissue Coincident with the widening of the blood vessels there is an *increase in the rate of blood flow* The inflamed tissue appears red and feels hot The local heat is due to increased vascularity and the failure of the blood to cool as it passes the more rapidly through the terminal radicles of the vascular system Together with the vascular change there is an *exudation of fluid* into the tissue and a *diape*

or less successful parenchymal regeneration create a confused picture The prolonged stubborn battle is carried out by the large mononuclears and the wandering cells (histiocytes macrophages reticulo endothelial cells and endothelial leukocytes) Suppuration does not occur commonly If it does take place the characteristic of the clinical manifestation is best expressed by the term *cold abscess* since there is no acute inflammatory redness or heat With breaking down of the protective skin or mucous membrane surface the exuberant reparative process in the connective tissue and the parenchyma gives the appearance of a *granuloma* If healing occurs there is an abundant fibrosis often so extensive as to embarrass the function of the organ leaving the victorious host alive but crippled

The chronic inflammatory process is characterized by its *long duration* and *its tendency to wax and wane* It is difficult for the clinician to ascertain when recovery has taken place and how soon a *recrudescence* or *relapse* may occur Quite extraneous incidents such as local trauma or the acquisition of an acute infection of an entirely different nature may disturb the balance in the chronic inflammatory process and produce a non specific activation These considerations make it difficult to evaluate therapy Was recovery a manifestation of the *vis mediatrix naturae?* Did it result from specific therapy? Was the exacerbation a manifestation of the natural history of the disease? Did it become activated by well intended therapy by trauma or by psychogenic influences?

DEFEAT OF THE HOST—In acute inflammatory disorders the local defenses may become routed and death occur from overwhelming *toxemia* or *sepsis* In the chronic states the sufferer dies of a prolonged *cachexia* or of a *functional impairment* due to loss of or irreparable damage to parenchymal tissue Despite the viability and resistance of the human body and the ministrations of modern medicine each human inevitably succumbs in the vital struggle leaving his progeny to carry on in his stead

FEVER

Body temperature in health is maintained as a constant variable as recorded by rectal thermometry (p 3484) Under normal conditions the low reading is noted in the morning within the range of 97° to 99° F and the high reading usually obtained in the afternoon registers between 98° and 100° F The daily variation in each subject rarely should exceed 1 F There is no way of knowing the individual range without making observations for several days but once the normal variation has been established it may be regarded as a constant

The facts relative to the registration of body temperature are at variance with the popular notion that the thermometer placed in the mouth should record 98 6° F (37 C) under normal conditions Oral temperatures may be misleading due to technical errors experience reveals that whereas 98 6° may be the average reading it is certainly not the normal reading for the vast majority of patients

Because of the great importance of registering body temperature the practitioner is urged to learn the normal rectal range for each of his patients in health Only in this way is it possible to ascertain minor but important deviations from the norm such as exist in relative pyrexia a term used to designate febrile disorders in which the thermometer read

material (amputation appendicectomy resection of gangrenous bowel), sacrificing the part to save the whole

RECOVERY —When the tissues of the host wage a successful battle the noxious invader or irritant is dissolved neutralized or phagocytized by the cellular defense The tissue fluid returns to the vascular lumen The caliber of the blood vessels and the blood flow are restored to normal Uncomplicated recovery has taken place

SUPPURATION —When the local struggle has been more prolonged and there are heavy casualties of local tissue cells and particularly of bacterial bodies gross manifestations of the lethal struggle become visible There are clear evidences of the formation of *pus* the systemic structures have been spared at the expense of local sacrifice Small abscesses *may resolve spontaneously* but more often the abscess will approach the surface and is *drained* by surgical incision It may burst through the protective membrane and spontaneously evacuate externally on a skin surface it may rupture internally as with an extension of a lung abscess into the pleural cavity In the one instance the effect is therapeutic and curative in the other previously uninvolved areas become contaminated in a widespread advance of the infective process

In suppurative processes the physician is called upon to manifest his most mature judgment *Premature incision* injures the inflammatory response and furthers the spread of infection along the path of instrumentation *Delayed intervention* as in appendicitis invites rupture of the localized process and spread of infection to clean tissue (peritonitis) Fortunate the patient and happy the physician when decisions as to therapy are made aptly and the procedure is executed with a nicety of technical skill

FIBROSIS —With the death of tissue the reparative process begins simultaneously and continues to operate after the cessation of the inflammatory portion of the defensive reaction Fibroblasts are laid down and the surviving parenchymal cells are stimulated to growth The latter being the more specialized and delicate may fail in their ability to regenerate Under such circumstances the area is filled in by connective tissue with resulting scar formation and fibrosis In certain organs such as the liver despite its enormous power of parenchymal regeneration fibrotic repair occurs after severe damage and gives rise to *hepatic cirrhosis* This is accompanied by impairment of hepatic function and often delayed death from hepatic insufficiency (p 1969)

CHRONIC INFLAMMATION —In inflammatory reactions that are less violent and which are caused by subtler influences than invoke the outpouring of the phagocytic leukocytes a slower and less tempestuous reaction occurs There may be little or no widening of the capillaries or alterations in the blood stream The polymorphonuclear leukocytes are not attracted to the part In their stead there arrive by slow stages swarms of mononuclear forms usually accompanied by the lymphocytes (Fig 5 p 17)

In the chronic inflammatory process the tempo of the active struggle is carried out at a pace that is so slow that repair occurs concurrently and side by side Thus the chronic inflammatory process is characterized histologically by the simultaneous appearance of the mononuclear cellular response and the fibroblastic reparative process These together with more

rare occasions hypopyrexia is created intentionally for therapeutic purposes in the course of crymotherapy (p 378) or *artificial refrigeration (p 3785)*

Acute Hypopyrexia —An acute fall in temperature to subnormal levels may be observed in febrile or afebrile patients Sudden hypopyrexia may be an early and important symptom of serious complications Following trauma or surgical procedures fall in temperature to subnormal levels occurs in shock perforation acute hemorrhage and collapse while in the diabetic it is an early sign of hypoglycemia The patient with peptic ulcer or gastric malignancy exhibits subnormal temperature as an accompani

DIFFERENTIAL DIAGNOSIS OF

Sustained Hypopyrexia

The maintenance of a rectal temperature that is consistently in the low range of 97° to 98° F or less has ominous connotation in chronic disease suggesting as it does depletion of the powers of host resistance or the overwhelming onslaught of the forces of destruction

CAUSE	DIAGNOSTIC FEATURES
Physiologic	Normal variant with starvation dehydration and inanition
Metabolic	Associated with the cachexias accompanying senility malignancy prolonged backward failure protracted chronic nephritis and arteriosclerosis
Infectious	Terminal stages of chronic invasion in children the aged, or debilitated
Endocrine	
Hypothyroidism	Cretinism and myxedema (p 1193) Low B M R. Responds to thyroid extract
Adrenal Cortical Deficiency	Addison s disease (p 1271) Hypotension, pigmentation and marked asthenia Specific response to sodium and adrenal cortical hormone (p 1267)
Anterior Pituitary Deficiency	Simmonds disease with extreme cachexia low B M P and x ray evidence of disturbance in region of sella turcica (p 1169) No therapeutic response to thyroid extract sodium or adrenal cortical extract
Neurogenic and Psychogenic Disorders	Neurasthenia (p 1300) and deterioration in the chronic neuropathies and psychoses (p 1364)

ment of massive exsanguination In the prolonged fevers sudden hypopyrexia suggests hidden hemorrhage forward failure or the completion of a crisis Subnormal temperatures often precede and follow sudden hyperpyrexia with chilling as particularly noted in vein infections such as sinus thrombosis or pylephlebitis See *Differential Diagnosis of Acute Hypopyrexia* (p 22)

In almost any circumstance acute hypopyrexia poses an urgent and difficult problem for the practitioner and one which must be resolved with utmost rapidity if indicated therapeutic measures are to be utilized to their full potential

ings do not exceed 100° F despite a diurnal variation in excess of 1° F (p 22) The practitioner who encounters febrile disorders in their incipiency must recognize and cope with relative pyrexia in diseases such as tuberculosis and rheumatic fever

The Physiology of Temperature Regulation—The control of body heat is maintained through thermostatic centers in midbrain and upper thoracic cord Sections of the neuraxis in these regions may result in loss of physical and/or chemical heat regulation Peripherally heat regulation is dependent upon functions of the involuntary nervous system and the glands of internal secretion particularly adrenals and thyroid Sympathetic influences are visible through dilatation or constriction of cutaneous vessels in response to changes in external environmental temperature the phenomenon of sweating occurs with excessive heat and pilomotor responses (goose-flesh) are seen during exposure to cold The clinician is aware of endocrine influences through hypothermia observed in cretinism and Addison s disease and a relative hyperthermia noted in hyperthyroidism

Body temperature in homoiothermic animals such as man represents the balance between heat production and heat loss Heat production results from chemical reactions mostly due to generation of warmth during the metabolism of foods or of body tissue Heat is lost by radiation convection and conduction mostly through the skin, evaporation of water from lungs and skin the necessity for warming inspired air the liberation of carbon dioxide from blood into lungs and the excretion of warmed urine and feces

Mechanisms of Heat Regulation—The mechanisms by which heat is produced and dissipated must be capable of rapid and wide adjustment since heat production and heat loss may have to be altered as much as 40 to 50 per cent for the maintenance of a constant body temperature In great part, the compensatory mechanisms are functions of tegumentary and nervous systems With elevation of external heat body temperature is held at normal by dilatation of skin vessels stimulation of sweat glands and increases in the rate and amplitude of respiration The reaction to external cold consists of constriction of skin vessels contraction of pilomotors and a general increase in muscle tonus which may eventually result in shivering

The Clinical Effects of Fever—Fever produces increases in basal metabolic rate respiratory and pulse rates and the work of the heart The patient usually complains of a feeling of warmth though chilling may accompany sudden changes of 4 to 5 F The febrile patient may be listless or restless and later may become stuporous comatose or delirious The motility of the digestive tract is inhibited by temperatures beyond 103 F as the result of which anorexia constipation dehydration and toxic ileus may be encountered

Antipyresis—Reduction of temperature may be accomplished by *hydrotherapy* (p 3791) or through the use of *antipyretic drugs* (p 3832) The philosophical implications of antipyresis are confusing Antipyretic measures are employed to combat the subjective complaints of the patient while hyperthermia (p 3789) is artificially induced for therapeutic purposes in the treatment of infectious diseases notably general paresis gonorrhea and chronic arthritides Conciliation of these opposing practices presents difficulties While antipyretic treatment adds to comfort there is little doubt that therapeutic hyperthermia stimulates the reticulo-endothelial system to greater phagocytic action increases the rate of formation of immune bodies impairs the viability of the invading organism and increases the efficacy of specific bactericides and antibiotic agencies The practitioner must choose whether to sacrifice the comfort of the patient or the defenses against invasion

CLINICAL DISTURBANCES OF HEAT REGULATION

The clinician is occasionally confronted with the problem of elucidating the cause for a sustained or sudden *hypopyrexia* but more frequent and complicated are those problems which deal with *fever* (p 19) Occasionally febrile disturbances are initiated or punctuated by *chilling* under which circumstance the practitioner is faced with a disturbance of more than ordinary urgency (p 31)

Subnormal Temperatures (Hypopyrexia)—Recording of subnormal temperature may be the result of some acute or protracted disturbance On

Afebrile Infections —Fever is usually but not invariably caused by the invasion of a pathogenic organism Afebrile infections are encountered when as in the common cold the pathogen arouses only mild and localized inflammatory disturbances They are seen in chronic disease when as in tuberculosis and syphilis the inflammatory processes are stalemated Much more ominous are afebrile infections of overwhelming intensity and those which attack an individual of markedly diminished resistance The former is illustrated by certain of the meningococcemias (p 211) whereas diminution in resistance is most often seen at the extremes of life in infants and the aged

Aseptic Pyrexias —Though elevation of temperature most often indicates the presence of an infection aseptic conditions may produce disturbances of heat regulation The most common examples include fictitious pyrexia pseudopyrexia neurogenic pyrexia physical pyrexia intravenous pyrogen injection and speed shock drug fevers poisonings fever due to endogenous metabolic disturbances and surgical manipulations anemic pyrexia hypostatic pyrexia fever due to intravascular accidents metastatic fevers fever due to imperviousness of the skin therapeutic hyperpyrexia and transfusion reactions The importance of the recognition of aseptic pyrexias is emphasized by their excellent prognosis and the therapeutic implications which involve elimination of the cause rather than the administration of chemotherapeutic and antibiotic agencies

Fictitious Pyrexia —Fictitious pyrexia may be found deliberately or unwittingly by failure to shake down a thermometer or by accidental or deliberate contact between mercury bulb and hot water bag or hot fluid Errors can be avoided if the physician shakes down the thermometer inserts it into the rectum and holds it until it is removed and read

False Pyrexia (*Pseudopyrexia*) —False or pseudopyrexia occurs when the thermometer reading is elevated though the patient is not actually febrile For example a rectal temperature taken immediately after a hot bath violent exercise or a bowel movement (or an oral temperature recorded after a warm drink) may show slight elevation in the reading These variables are best classified as pseudopyrexias and they must not be interpreted as evidences that the patient is ill

Neurogenic Pyrexias —In infancy and childhood crying and tantrums may produce increased thermometer readings due to neurogenic fluctuations of the labile temperature-regulating centers *Thalamic fever* an extremely rare neurogenic phenomenon is usually due to hemorrhage in the regions of basal ganglia or pons

So called *sympathetic fever* occasionally may be seen in unstable patients usually young women For long periods of time the thermometer reading may rise to 101° F with a diurnal fluctuation of 1.5 to 2 despite perfect health Chronic infection particularly tuberculosis must always be suspected and evidences are meticulously and repeatedly sought If no pathological condition is discovered and the pyrexia is compatible with complete well being the optimum form of therapy is discontinuance of observation and resumption of normal activity

Physical Pyrexia —Pyrexia of purely physical origin occurs with trauma or exposure to the sun In *heat stroke* the temperature may rise alarmingly and death may occur unless therapy is prompt The tempera

Fever (Pyrexia)—Elevation of body temperature is *relative* if the diurnal variation exceeds 1° F even when the high reading does not touch 100° F *Absolute pyrexia* exists when the temperature rises beyond 100° F at any time during the twenty four hours

DIFFERENTIAL DIAGNOSIS OF

Acute Hypopyrexia

In acute hypopyrexia the rectal temperature may be below 90° F most often however the readings are in the neighborhood of 92 to 94 F

CAUSE	DIAGNOSTIC FEATURES
Physiologic	Following immersion and exposure to severe cold
Poisoning	From overdosage or idiosyncrasy to a general anesthetic opiate (p 3853) barbiturate (p 3839) alcohol (p 3847) or antipyretic (p 3832)
Metabolic	In all conditions associated with coma (p 1294) In hypoglycemic shock due to over dosage with insulin (p 1241) In uremia (p 227b) and the crises of Addison s disease (p 1275) Therapeutic test with dextrose and epinephrine in suspected hypoglycemia Give sodium and adrenal cortical extract in Addison s disease
Allergic	Anaphylactic shock (p 549) Prepare for intravenous intra-arterial and intracardiac injections of epinephrine (p 3877)
Forward Failure	In all conditions associated with syncope (p 921) and shock (p 928) Note falling gradient of blood pressure rising pulse rate and increased hematocrit readings (p 3707) Prepare for plasma infusions (p 3778) and oral or intravenous sodium lactate (p 3775)
Hemorrhage	With massive exsanguinations (may be occult) Note falling gradient of blood pressure and relatively more rapid elevation of pulse rate Hematocrit readings decreased (p 3707) Attempt hemostasis by surgical means if necessary Prepare for transfusion (p 3778) while starting saline or plasma infusion.
Infection	Post-critical Preceding or following chill With overwhelming infection Obtain blood culture and prepare for intensive probatory antibiotic therapy particularly with penicillin (p 113) or streptomycin (p 104)

Fever may be observed in the individual who has previously enjoyed normal health It may occur in the patient who is recovering from an operation or childbirth or in one afflicted with chronic illness It may accompany traumatic experiences such as injury by physical or chemical modalities

cystoscopy and of the latter the transitory elevation that accompanies laparotomy craniotomy or thoracotomy

Anemic Pyrexia —Aseptic fever may occur in the anemias (p 1055) and leukemias (p 1100) In pernicious anemia the return of the blood count to normal will often be accompanied by a lowering of the temperature an average of a degree or more (p 1077) Elevation of temperature without infection is observed in the leukemias particularly those of the acute variety

Hypostatic Pyrexia —Hypostasis in the decompensated cardiac patient (p 943) may produce pyrexia in the absence of infection The tempera ture elevation rarely exceeds 101 F unless a bacterial pneumonitis has been superimposed

Fever Due to Intravascular Accidents —Fever characterizes sterile intra vascular circulatory accidents such as *embolization* (p 977) *phlebitis* (p 1123) and *coronary thrombosis* (p 983) The febrile elevation may reach 103° F and may persist for several days

Neoplastic Fever —Fever is associated with metastatic malignancy par ticularly miliary carcinomatosis of the lungs (p 2081) It also accom panies primary growths in bone (p 2845) kidneys (p 2328) and stomach even before ulceration and infection have occurred

Fever Due to Imperviousness of the Skin —In scleroderma (p 3427) heat loss is prevented by the hidebound character of the tegumentary system and aseptic fever is frequently recorded

Therapeutic Hyperpyrexias —Artificial or therapeutic hyperpyrexia may be produced by diathermy a hot bath hot blankets and the hypertherm (p 3789) It is also accomplished through parenteral administration of protein or protein split products such as typhoid vaccine boiled milk and peptone (p 3789)

Transfusion Reactions —Blood transfusions frequently are followed by sterile pyrexias due to minor alterations in blood matching or the presence of food protein in the circulating fluid To prevent reactions the donor should be fasted for eight hours before phlebotomy (p 852) and his blood must be cross matched (p 3711) with that of the recipient

Fever of Infectious Origin —The majority of infections are accompanied by fever which may be relative or absolute In rare instances elevation of temperature is the only physical finding The *cryptogenic infections* are summarized in table form on p 26 With increasing frequency febrile disturbances may be diagnosed by *laboratory methods* which should be fully exploited by the enlightened clinician (p 30) In the vast majority of cases the clue to the etiology of the febrile disturbance is afforded by an accompanying *subjective complaint* usually pain or an *objective find ing* that is elicited during the course of the physical examination Under these last circumstances as delineated on p 172 the diagnostic problem is of more limited scope since it involves closer scrutiny of the indicated tissue for evidences of purely local inflammation or of a local manifestation of a systemic process

Difficulties of Investigating Febrile Processes in Private Practice —In pri vate practice the investigation of the cause of a febrile disturbance pre sents many more difficulties than in institutional medicine In the first

DIFFERENTIAL DIAGNOSIS OF

Cryptogenic Fever

Cryptogenic fever provides the greatest challenge to the acumen of the practitioner Without localizing clues he is compelled to resort to repeated examinations the performance of a battery of laboratory tests investigation of epidemiologic data and finally the therapeutic test of ascertaining the reaction of his patient to specific drugs and antibiotic agencies

CAUSE	DIAGNOSTIC FEATURES
Aseptic Pyrexia	See p 23
Systemic Coccal Invasion	*Staphylococcemia streptococcemia rheumatic fever meningococcemia and gonococcemia* Blood cultures positive Specific response of rheumatic fever to salicylate (p 194) of other infections to sulfonamide (p 88) and penicillin (p 106)
Systemic Bacillary Invasion	*Blood cultures positive (E typhi salmonella S dysenteriae E coli B melitensis (brucellosis) and Pasteurella tularensis* Serum agglutinin tests for typhoid fever salmonella dysentery and colon bacilli (p 245) Skin tests in brucellosis tularemia tuberculosis and leprosy X ray chest Stool and urine cultures (p 54) Try streptomycin (p 104)
Systemic Spirochetal Invasion	Serologic tests for syphilis (p 337) special search of blood spreads in relapsing fever (p 357) Probatory therapy with penicillin or arsenical (p 113)
Systemic Rickettsial Invasion	*Typhus Rocky Mountain Spotted Fever and tsutsugamushi fever* History of louse or tick bite Perform Weil Felix reactions (p 372)
Systemic Virus Infections	*Infectious mononucleosis* lymphocytosis or leukopenia (p 50) Get hemogram (p 3692) and blood for heterophile reaction (p 468) *Psittacosis and ornithosis* History of handling sick bird. Perform complement fixation tests (p 59)
Systemic Fungus Infections	*Actinomycosis and coccidioidomycosis* (p 499) Perform skin reactions and look for lesion to obtain material for direct examination.
Systemic Protozoal Infections	*Malaria* (p 507) Examine thick and thin blood smears and sternal marrow (p 510) Try therapeutic tests with quinine (p 516)
Systemic Helminthic Infections	*Trichinosis* (p 539) Look for eosinophilia (p 542) Do skin tests (p 59) History of eating uncooked pork
Focal Infection	Particularly in teeth, tonsils and nasal accessory sinuses
Occult Localized Infection	In paranasal sinuses prostate perinephric region, kidney (renal carbuncle) renal pelvis (pyelitis) liver (amebic hydatid or nonspecific abscess) pelvic peritoneum (post abortal gonorrheal or post partum infection) fallopian tubes (particularly tuberculous gonorrheal or post-abortal salpingitis) lungs (particularly pulmonary tuberculosis atypical pneumonia

mycoses or abscess) and endocardium (subacute bacterial endocarditis)
Make repeated intensive physical examinations Attempt to visualize suspected structure or area by direct or contrast radiography (p 3742) Diagnostic lavage or aspiration where possible (p 2023)
Obtain specimens by endoscopy (p 2025) if structure communicates with external orifices (cystoscopy bronchoscopy)

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place the clinician commonly sees his patient shortly after the onset of the fever when there may be few if any localizing signs The patient with pneumonia is examined after the initial chill and before there are present in the lungs the classical signs of consolidation the exanthems are often viewed in the pre eruptive phase and the abdomen is examined in acute appendicitis before peritoneal phenomena have developed (p 1882) Institutional physicians who later see the full blown syndrome might be less critical of the local practitioner were they to realize the importance of time relationship Often the much criticized clinician indulges in silent speculation as to how much better the Monday morning quarterbacks might have done had they been calling the plays of the previous Saturday afternoon

A second great handicap under which the practitioner operates particularly in relationship to the institutional physician is the impracticability of making complete laboratory examinations on each febrile patient The realist appreciates the fact that the majority of febrile disturbances are acute benign and of short duration He knows also that it is not humanly possible to make a complete survey of each febrile patient no matter how great the desirability Also he is aware of the fact that many laboratory examinations notably blood cultures are positive only in the first few hours or days of the illness and that taken later the golden opportunity already has passed Finally the not altogether minor aspect of economics enters into the diagnostic survey since the added burden of unlimited though worthy tests might well be beyond the resources of the family All of which adds up to the fact that beyond routine urinalysis and a hemogram the practitioner has not the advantage of laboratory aid in the investigation of a febrile illness unless the disturbance is of more than moderate severity of increasing intensity or of a duration beyond a few days

The technics of laboratory diagnosis are elaborated on pages 3609 to 3743 Reverence for laboratory data must not blind the practitioner to the fact that even medical science has its limitations The clinical pathologist does not make the diagnosis he merely reports his finding and the clinician interprets that information with particular reference to his individual patient *Positive findings* naturally are of the greatest value but the fact that there are high agglutinins for typhoid fever does not prove that the patient is afflicted with that malady it takes more than a positive skin reaction to tuberculin to prove that the patient suffers from tuberculosis and more than pyuria to establish the presence of active urinary tract infection

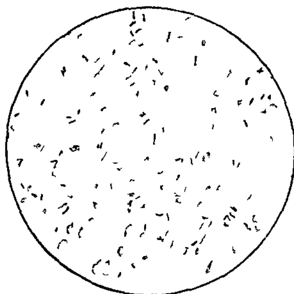
DIFFERENTIAL DIAGNOSIS OF

Relapsing Fevers

In the majority of cases a return of fever indicates the development of some complication uch as for example empyema following lobar pneumonia or of the interpolation of an a eptic pyrexia most likely a drug fever due to sulfonamide (p 94) If the e phenomena can be excluded the clinician recognizes that he is dealing with some type of relapsing fever

CAUSE	DIAGNOSTIC FEATURES
Rheumatic Fever	Relapses especially frequent in the spring Joint manifestations and carditis Specific therapy with salicylates (p 194)
Typhoid Fever	Initial attack may be followed by relapse of lesser intensity and duration (p 232) Repeat blood culture and agglutination tests
Brucellosis	Irregular relap es as encountered in cla sical Malta fever (p 316) Perform skin test (p 317)
Relapsing Fever	Spirochetal invasion with initial febrile period of 4 to 10 days and one or everal repetitions in 1 or 2 weeks (p 359) History of louse or tick bite Spirochetes in blood mears or urine sediment (p 359)
Infectious Jaundice	Initial febrile period of 3 to 4 days with a sec ond rise in the second week usually accom panied by jaundice (p 1979) History of contact with rats as in sewer work Spirochetes in blood and urine (p 360)
Rat Bite Fever	Hi tory of rat bite Initial febrile period of 3 or 4 days with second rise in the second week (p 363)
Trench Fever	Two or more febrile episodes of mild and be nign character (p 383) History of exposure
Bullis Fever	Two or more brief febrile epi odes following tick bite (p 383) History of exposure
Colorado Tick Fever	Two or more brief febrile episodes of a benign character (p 384) History of tick bite
Dengue Fever	Saddle back fever of brief duration (p 406) Hi tory of fly bite and epidemic
Poliomyelitis	Saddle back fever with initial preparalytic stage and second bout accompanied by neuro logic manifestations (p 457) Obtain cere brospinal fluid. Send serum for virus neutral izing bodies (p 60)
Yellow Fever	Initial febrile episode with brief intermission and secondary bout with jaundice (p 477) History of mosquito bite Send serum for virus neutralizing bodies (p 60)
Malaria	Recurrent chills and fevers at 2-day intervals in tertian invasion, and at 3-day intervals in quartan infection (p 513, Marked irregular ity with mixed infections and in falciparum malaria (p 514) Search blood and sternal marrow for plasmodia Observe response to therapeutic test with quinine (p 516)

Leishmaniasis	Irregular febrile bouts with irregular relapses at repeated intervals (p 534) Perform agglutinin and skin tests (p 60) Get specimens from local lesions lymph nodes spleen or bone marrow for identification of Leishman Donovan bodies (p 48)



A



B

Fig 6—Stained demonstration of pathogens *A* *Mycobacterium tuberculosis* from sputum (Cornet and Meyer) *B* *Treponema pallidum* from tissues in neonatal syphilis (Sobernheim in Kolle and Wassermann)

LABORATORY AIDS IN DIAGNOSIS OF

Infectious Fevers

SPECIMEN	LABORATORY PROCEDURE
Material from Lesion	Examine unstained specimen microscopically for fungi amebas ova and parasites (p 50)
	Darkfield microscopy for spirochetes (p 45)
	Gram stain for ordinary cocci and bacilli (p 52)
	Carbolfuchsin stain for tubercle bacilli (p 52)
	Loeffler stain for C diphtheriae (p 308)
	Spore stain for anthrax and tetanus (p 52)
	Capsule stain for pneumococcus and Friedlander bacillus (p 52)
	Wright stain for Donovan bodies (p 47b) Leishman Donovan bodies (p 535) trypanosomes (p 531) spirochetes (p 45) and malarial parasites (p 508)
Blood Smear	Wright stain for differential count of leukocytes and identification of malarial parasites (p 510) trypanosomes (p 535) and spirochetes (p 50)
Urine	Carbolfuchsin stain of concentrated specimen for tubercle bacilli (p 52)
	Darkfield microscopy for spirochetes (p 45)
	Microscopy for helminthic ova (p 1894)
Stool	Warm stage microscopy for amebas Direct microscopy for helminthic ova and parasites Carbolfuchsin stain of concentrated specimen for tubercle bacilli particularly in children (p 52)
Cerebrospinal Fluid	Cell count for leukocytes Sugar and protein tests Gram stain for predominant organism (p 52) Carbolfuchsin stain of concentrated specimen for tubercle bacilli (p 52) Wright stain for differential leukocyte count
	Darkfield microscopy for spirochetes (p 45)
Sternal Marrow	Wright stain for cytology and identification of malarial parasite and Leishman Donovan bodies
Pus Discharge and Material from Aspiration	Gram stain for predominant organism (p 52) Darkfield microscopy for pirochetes (p 45) Wright stain for Donovan and Leishman Donovan bodies (p 48)
	Pappenheim stain for H ducreyi (chancroid)
Hemogram	For leukocytosis (p 1097) lymphocytosis (p 1098) leukopenia (p 471) eosinophilia (p 542) monocytosis (p 1099) anemia (p 1055) and thrombocytopenia (p 1114)
Blood Culture	Particularly for coccal and bacillary invaders (p 54)
Cultures of Urine Stool Sputum Cerebrospinal Fluid Pus and Exudate	Identification of predominant organism (p 54)

Blood Serum	For titer of specific agglutinin (p 59) precipitins (p 59) complement fixing and virus neutralizing bodies (p 59)
Skin Tests	Particularly in brucellosis chancroid echinococcus lymphopathia venereum, scarlet fever trichinosis trichophytosis tuberculosis and tularemia (p 59)
Animal Inoculation Tests	Specialist procedures Particularly in rickettsial and virus diseases (p 62) and tuberculosis (p 62)

Negative data do not preclude the possibility of inflammation due to infection a normal blood count does not eliminate the possibility of deep seated localized suppuration as for example an appendiceal abscess a sterile blood culture may be obtained in typhoid fever subacute bacterial endocarditis or any other of the bacteremias a negative Wassermann is the expectancy rather than the rule in the primary weeks of syphilis it may take many long hours before acid fast bacilli can be found in sputum or spinal fluid despite fairly clear cut evidences respectively of pulmonary or meningeal tuberculosis

Infections Recognized by Specific Laboratory Tests—The science of medical diagnosis in fevers due to infectious disease provides the clinician with eminently satisfactory laboratory procedures by which he may recognize the condition with which he is dealing and follow the progress of events Certain of the reactions such as bacteremia leave no doubt as to the significance of the information others like agglutination and complement fixation tests must be correlated with clinical and immunologic data Negative tests with suggestive clinical findings require repetition positive tests which cannot be correlated with the clinical syndrome need checking

Inasmuch as the clue to the diagnosis resides in the laboratory finding rather than the nature of the temperature curve the reader is referred to the discussions on the following pages for more definitive information

Infectious Fevers with Pathognomonic or Suggestive Clinical Manifestations—In clinical practice the majority of infectious fevers are diagnosed as the result of clues furnished by suggestive or pathognomonic clinical manifestations This situation particularly prevails in acute and benign invasions The practitioner rarely invokes laboratory assistance in committing himself to the diagnosis of the common cold influenza gastro enteritis or an attack of one of the eruptive diseases (p 172) In these instances his reliance is placed upon the subjective complaint or objective finding If he encounters difficulty in the establishment of the diagnosis his main assistance is derived from the *localizing phenomenon* such as pain lymphadenopathy splenomegaly pyuria nasal discharge hemoptysis hoarseness diarrhea vomiting jaundice a urethral or vaginal discharge joint swelling bone tenderness and the like Fever is a nonspecific finding hence the reader is referred to the differential diagnosis of the presenting symptom or sign rather than to the disturbance in heat regulation

Fever with Chills—As in the instance of fever chills may be of aseptic or infectious origin In the latter instance chilling may be present at the onset of an acute infection it may occur irregularly during the course of

DIFFERENTIAL DIAGNOSIS OF

Chills

The patient who suffers from an infectious di ease which is characterized by chills is sufficiently ill in most instances so that hospitalization is required for necessary laboratory investigations specialist consultation and intensive therapy Particularly with suspected vein involvement surgical consultation is encouraged in order to be prepared for drainage of a localized collection of pus or ligation of an accessible vein that is serving as a feeding focus

CAUSE	DIAGNOSTIC FEATURES
Aseptic	Follows instrumentation, such as catheterization or the passage of sounds and cystoscopy Due to errors in cross matching in transfusion (p 3710) pyrogens in infusion material foreign protein in immune serum peed shock (p 924)
Systemic Coccal Invasion	Blood cultures show staphylococci streptococci pneumococci meningococci or gonococci
Systemic Bacillary Invasion	Rare occurrence in E coli bacteremia tularemia and brucellosis
Systemic Rickettsial Invasion	In typhus and spotted fevers (p 369) Get Weil Felix reactions
Systemic Virus Invasion	In influenza dengue infectious mononucleosis and yellow fever
Systemic Protozoal Invasion	Malaria (p 507) Identify pla modium in the blood smear Therapeutic test with quinine (p 516)
Predominantly Local Infection and Suppuration	
Intravascular	With suppurative endophlebitis involving lateral jugular or cavernous sinu es (Get blood culture and consult otologist, ophthalmologist or rhinologist) With peripheral endophlebitis and pylephlebitis embolization and thromboses lymphangitis and lymphadenitis
Endocarditic	In acute and subacute bacterial endocarditis (p 1020) Blood cultures positive (p 54)
Neurogenic	In meningitis (p 1462) and brain abscess (p 1469) Spinal fluid positive
Hepatic	In gangrenous cholecystitis suppurative cholangitis and liver abscess (p 1980)
Peritoneal	In acute peritonitis (p 1923) and subdiaphragmatic subphrenic or peritoneal absces es (p 1927)
Pleuropulmonary	In acute fibrinous pleurisy empyema thoracis rupture of lung absce s on.et of lobar pneumonia spread of lobar pneumonia or pulmonary infarction (p 2080) X rays and sputum positive Examine pleural fluid
Rhinogenic	In suppurative spheno-ethmoiditis and rhinogenic meningitis (p 2125) X rays and spinal fluid positive
Otogenic	In mastoiditis labyrinthitis petrositis and otogenic meningitis (p 2147) X rays spinal fluid and blood and ear cultures positive

Renal	In pyelitis perinephric abscess renal carbuncle and pyelonephritis (p 2353) Blood and urine cultures positive Prepare for urologic survey
Gynecologic	In post abortal and puerperal septic endometritis and pelvic peritonitis (p 2602) Blood culture positive
Osseous	At onset or spread of osteomyelitis (p 2930) X rays and blood cultures positive
Hematologic	Posttransfusion (p 3779) In lymphoblastoma (p 1137) and Hodgkin s disease (p 1138) Sternal marrow or biopsy positive (p 1043)

the disease it may herald the onset of a complication or finally it may be recurrent at periodic or indefinite intervals

Aseptic chilling usually results from the introduction of a foreign protein into the blood stream More concretely the offending substance may be a pyrogen the product of an error in matching of transfused blood a bacterium introduced during instrumentation particularly cystoscopy or an immune body or killed vaccine injected for therapeutic purposes (p 76)

The chill that occurs at the onset of an infection usually means that there has been an acute elevation of temperature in excess of 4° or 5 F Most often this occurs in tempestuous coccal invasions with pneumococcus or meningococcus but it may be experienced also in bacillary disorders such as influenza or protozoal afflictions such as malaria Chilling during the course of an infectious disease usually signifies a complicating process such as a spread to another lobe in pneumonia or bursting of the peritoneal barrier in appendicitis Recurrent chilling suggests most strongly that the patient is suffering from a malaria or from vein or endocardial infection Illustrative of the latter are sinus thrombosis pylephlebitis and subacute bacterial endocarditis

gories to invaders whose places are not quite clear Thus the streptobacillus of Haverhill fever is listed with spirochetal infections the *Bartonella bacilliformis* of verruga peruana is included with the rickettsia and histoplasmosis is found among the deep fungus invaders

The majority of the infectious states are described in the present section in order to emphasize that it is the host as an entity who is afflicted rather than any single tissue or organ Thus *gonorrhea* is regarded as a systemic disease and not a mere urethral inflammation *meningococcic meningitis* is a total invasion and its consequences are not confined to the covering of the nervous system The great accomplishments of specific anti infective therapy have pointed up the wisdom of this viewpoint most particularly with regard to pneumonia meningitis and gonorrhea in each of these processes the therapeutic attack is best conducted through treatment of the patient rather than his individual organ or organs In certain other instances however clarity of presentation has demanded that the infectious condition be described in relationship to the structure most involved the pyoderms superficial fungous infections cutaneous manifestations of leishmaniasis and some of the virus infections (warts molluscum contagiosum and herpes) appear in the section on the *Tegumentary Diseases* afflictions due to the Koch Weeks bacillus the Morax Axenfeld organisms and the viruses that cause trachoma inclusion blennorrhea and epidemic keratoconjunctivitis are included in the section on *Ophthalmology* the helminthic infestations of the bowel are found in the section on the *Digestive System*

Bacteria (p 137)
- The Gram positive Cocci (p 151)
  - Staphylococcus
  - Streptococcus
  - Pneumococcus (*Diplococcus pneumoniae*)
- The Neisseriaceae (Gram negative Cocci) (p 208)
  - Meningococcus (*N intracellularis*)
  - Gonococcus (*N gonorrhoeae*)
- The Enteric Bacilli (Gram negative Bacilli) (p 225)
  - Typhoid (*Eberthella typhosa*)
  - Paratyphoid (*Salmonellae*)
  - Dysentery (*Shigellae*)
  - Colon (*Escherichia coli*)
  - Cholera (*Vibrio comma*)
- The Mycobacteriaceae (Acid fast Bacilli) (p 2 9)
  - Tuberculosis (*M tuberculosis*)
  - Leprosy (*M leprae*)
- The Hemophileae (Gram negative Bacilli) (p 2 8)
  - Pertussis (*H pertussis*)
  - Influenza (*H influenzae*)
  - Chancroid (*H ducreyi*)
  - Koch Weeks (*H conjunctivitidis*) see Ophthalmology (p 1621)
  - Morax Axenfeld (*H duplex*) see Ophthalmology (p 16 2)

Bacillus Anthracis Clostridia and Corynebacteria (Gram positive spore bearers) (p 2 2)
- Anthrax (*B anthracis*)
- Tetanus (*Cl tetani*)
- Gas Gangrene (*Cl perfringens etc*)
- Diphtheria (*Co diphtheriae*)
- Botul[illegible] *botulinum*)

- The Pasteurelleae and Brucelleae (Gram negative Bacilli) (p 314)
  - Melitensis (*Br melitensis*)
  - Plague (*P pestis*)
  - Tularensis (*P tularensis*)
- Miscellaneous (p 327)
  - Glanders (*Malleomyces mallei*)
  - *B mucosus capsulatus* (*Klebsiella pneumoniae* of Friedländer)
  - Erysipeloid (*Erysipelothrix rhusiopathiae*)
  - *B pyocyaneus* (*Pseudomonas aeruginosa*)
- Spirochetes (p 329)
  - Treponema (p 331)
    - Syphilis (*Treponema pallidum*)
    - Frambesia (*Treponema pertenue*)
    - Pinta (*Treponema carateum*)
  - Borrelia Leptospira and Spirilla (p 3)
    - Fusospirochetosis (*Borrelia vincentii*)
    - Relapsing Fever (*Borrelia recurrentis*)
    - Infectious Jaundice (*Leptospira icterohaemorrhagiae*)
    - Rat Bite Fever
    - Sodoku (*Spirillum minus*)
    - Haverhill Fever (*Streptobacillus moniliformis*)
- Rickettsia (p 366)
  - Typhus Fever
    - Endemic (*Rickettsia prowazeki*)
    - Murine (*Rickettsia mooseri*)
  - Rocky Mountain Spotted Fever (*Rickettsia rickettsii*)
  - Tsutsugamushi Diseases (*Rickettsia orientalis*)
  - Q Fever (*Rickettsia burneti*)
  - Trench Fever
  - Bull's Fever
  - Boutonneuse Fever
  - Colorado Tick Fever
  - Verruga Peruana (*Bartonella bacilliformis*)
  - Kew Gardens Spotted Fever
- Viruses (p 387)
  - Respiratory (p 391)
    - The Common Cold
    - Influenza
    - Atypical Pneumonia
    - Epidemic Pleurodynia
    - Dengue Fever
    - Dengue like Fevers
  - Dermotropic (p 40)
    - Measles
    - Rubella
    - Fourth Disease
    - Fifth Disease (Erythema Infectiosum)
    - Sixth Disease (Erythema Subitum)
    - Chickenpox
    - Smallpox
    - Vaccinia
    - Molluscum Contagiosum
    - Warts
    - Herpes Simplex
    - Herpes Zoster
    - Miliary Fever
    - Foot and Mouth Disease
    - Trachoma (p 16 5)
    - Inclusion Blennorrhea (p 16 3)
    - Epidemic Keratoconjunctivitis (p 16 4)

Neurotropic (p 439)
Rabies
Epidemic Encephalitis
Japanese Encephalitis
Russian Seasonal Encephalitis
Lymphocytic Choriomeningitis
Equine Encephalomyelitis
St Louis Encephalitis
Acute Anterior Poliomyelitis
Postinfectious Encephalitis
Miscellaneous (p 466)
Infectious Mononucleosis
Infectious Lymphocytosis
Infectious Leukopenia
Lymphopathia Venereum
Psittacosis
Ornithosis
Granuloma Inguinale
Yellow Fever
Mumps
Phlebotomus Fever (Sand Fly)
Reiter s Disease
Catarrhal Jaundice (*Infectious Hepatitis*) (p 1979)
Fungi (p 489)
Fungous Infections of the Skin (p 3993 in Diseases of Tegumentary System)
Chromoblastomycosis (*Hormodendrum pedrosoi*)
Erythrasma (*Microsporon minutissimum*)
Favus (*Achorion Schoenleinii*)
Maduromycosis (Mycetoma) (Actinomyces)
Moniliasis (*Monilia albicans*)
Paracoccidioidal Granuloma (Almeida s Disease) (*Paracoccidioides brasiliensis*)
Ringworm of the Auditory Canal (Aspergillus or Monilia)
Ringworm of the Axilla (Actinomyces)
Ringworm of the Beard (*Microsporon lanosum* or Trichophyton)
Ringworm of the Body (Microsporon or Trichophyton)
Ringworm of the Feet (*Trichophyton gypseum* or *purpureum*)
Ringworm of the Groin (*Epidermophyton inguinale*)
Ringworm of the Nails (*Monilia albicans Achorion schoenleinii* or Trichophyton)
Ringworm of the Scalp (*Microsporon lanosum* or *audouini*)
Tinea Imbricata (Endodermophyton)
Tinea Versicolor (Chromophytosis) (*Microsporon furfur*)
Systemic Fungous Infections (p 489)
Actinomycosis (Actinomyces)
Blastomycosis (Blastomyces)
Sporotrichosis (*Sporotrichum schenkii*)
Torulosis (*Torula histolytica*)
Aspergillosis (Aspergillus)
Coccidioidomycosis (*Coccidioides immitis*)
Moniliasis (*Monilia albicans*)
Histoplasmosis
Geotrichosis
Penicilliosis
Rhinosporidiosis
Protozoa (p 506)
Malaria (*Plasmodium falciparum vivax malariae* or *ovale*)
Amebiasis (*Endamoeba histolytica*)
Giardiasis (*Giardia lamblia*) see Digestive System (p 1892)
Trichomonas (*Trichomonas vaginalis*) see Female Reproductive System (p 2598)
Balantidiasis (*Balantidium coli*) see Digestive System (p 1893)
Leishmaniasis (*Leishmania donovani infantum tropica* or *brasiliensis*)
Trypanosomiasis (*Trypanosoma cruzi gambiense* or *rhodesiense*)
Toxoplasmosis

Helminthes (p 537)

Nematoda (Roundworms)

- *Ascaris lumbricoides* see Digestive System (p 1906)
- *Trichocephalus trichiurus* (Whipworm) see Digestive System (p 1906)
- *Necator americanus* (Hookworm) see Digestive System (p 1903)
- *Ancylostoma duodenale* (Hookworm) see Digestive System (p 1903)
- *Strongyloides stercoralis* (Threadworm) see Digestive System (p 1905)
- *Enterobius vermicularis* (Pinworm Seatworm Oxyuris) see Digestive System (p 1902)
- *Trichinella spiralis* (Trichinosis)
- *Wuchereria bancrofti* (Microfilaria) see Tegumentary System (p 3321)
- *Onchocerca volvulus* (Blinding Filaria) see Tegumentary System (p 3326)
- Loa loa (Loa or eye worm) see Tegumentary System (p 33 5)
- *Dracunculus medinensis* (Dragon Guinea or Medina Worm) see Tegumentary System (p 3328)

Platyhelminthes (Flatworms)

Cestoda (Tapeworms)

- *Diphyllobothrium latum* (Fish Tapeworm) see Digestive System (p 1899)
- *D mansoni* see Digestive System (p 1899)
- *Hymenolepis nana* (Dwarf Tapeworm) see Digestive System (p 1899)
- *Taenia saginata* (Beef Tapeworm) see Digestive System (p 1899)
- *Taenia solium* (Pork Tapeworm) see Digestive System (p 1899)
- *Echinococcus granulosus* (Hydatid Cyst) see Liver (p 1083)

Trematoda (Flukes)

- *Schistosoma japonicum* (Oriental Blood Fluke) see Tegumentary System (p 3195)
- *S mansoni* (Blood Fluke)
- *S haematobium* (Vesical Blood Fluke Bilharzia) see Urinary System (p 2341)
- *Fasciolopsis buski* (Giant Intestinal Fluke)
- *Clonorchis sinensis* (Chinese Liver Fluke) see Liver (p 198[illegible])
- *Paragonimus westermani* (Oriental Lung Fluke) see Lung (p 2[illegible]13)

Medical Entomology — Bugs are capable of producing local irritations of the skin (p 3180) which have mostly nuisance value Of much greater medical significance is the role of the insect as a disease *vector* transmitting highly pathogenic micro organisms from intermediate host or from infected man to man In malaria and yellow fever for example the mosquito is the infectious reservoir and the efforts of the entomologist are directed toward eradication of the insect (Table 2 p 42)

Tick Bite and Paralysis —In addition to the introduction of pathogens the bite of the female tick may cause fever and paralysis as the result of toxin formation Removal of the tick is followed by subsidence of fever and restoration of normal function

THE INFECTIOUS STATE

In contrast to the innocuous conditions associated with bacterial commensalism and symbiosis micro organisms may invade the tissues and produce disease The clinical manifestation of the invasion is the infectious state which results from increase in bacterial virulence and/or defects in body defenses The manifestations of infection may be many and varied there may be local or more generalized invasions

The Portal of Entry —The infectious lesion in and of itself may be of minor importance and yet serve as a portal of entry for serious systemic disease The management of such a process as illustrated by the *syphilitic chancre* stresses the recognition of the significance of the local lesion as a preliminary to the accomplishment of intensive systemic treatment

Local Infections—The local infection is one which has circumscribed significance as illustrated by the simple abscess or furuncle For the most part local infections are treated by external measures systemic treatment being employed for prophylaxis or the control of complications

Remote Local Infections—Certain of the systemic infections produce remote local manifestations This is illustrated particularly by the *metastatic furuncles* that result secondarily from *staphylococcemia* The secondary or metastatic foci may act as continuing bacterial sources after the primary lesion has been healed or excised They require active local treatment combined with vigorous systemic therapy

TABLE 2—INSECTS AS VECTORS OF DISEASE

Vectors	Diseases
Lice	
Pediculus capitis (head louse)	Typhus fever
Pediculus corporis (body louse)	Relapsing fever
Fleas	
Xenopsylla cheopis	Plague
Flies	
Phlebotomus (sandfly)	Dengue-like fevers verruga peruana leishmaniasis sandfly fever
Buffalo gnats (blackflies)	Onchocercosis
Chrysops (blood-sucking fly)	Loaiasis tularemia
Tabanus (blood sucking horse fly)	Anthrax trypanosomiasis
Stomoxyidae (muscoid house or latrine fly)	Typhoid and enteric fevers
Glossinidae (tsetse flies)	African trypanosomiasis
Mosquitoes	
Anopheles mosquito	Malaria
Culex mosquito	St Louis encephalitis filariasis equine encephalomyelitis
Aedes mosquito	Yellow fever dengue
Mites	
Biting mites	Filariasis
Liponyssus	Epidemic typhus
Trombicula	Tsutsugamushi fever
Eye gnats	Eye infections yaws
Cimex rotundatus	Kala azar
Triatoma	Trypanosomiasis
Ticks	
Dermacentor andersoni (Wood tick)	Rocky Mountain spotted fever tularemia
Soft body ticks	Relapsing fever

Focal Infections—The focal infection is a variety of the localized inflammatory process It differs from the simpler lesion in that it serves as a site of toxin production resulting in remote tissue disturbances Thus diphtheria bacilli lodge in the membranous inflammatory exudate of the naso

pharynx The organisms do not enter the blood stream but the diphtheria toxin produced at the local site damages the heart muscle and the peripheral nerves The therapeutic attack is directed towards amelioration of the noxious distant effects through administration of antitoxin

More chronic manifestations of focal infection are of a less tangible nature and have to do with such lesions as tonsillar and periodontal abscesses producing distant derangements particularly myalgias and arthropathies In dealing with these afflictions the practitioner aims to extirpate the focus Antitoxic therapy is futile and the distant manifestations require only palliative attention

Generalized Infections —The generalized infections are of variable nature The *toxemias* occur with sterile blood cultures when soluble exotoxin is manufactured by the invading organism at a local site The therapeutic attack is by injection of antitoxin where available

A *bacteremia* characterized by positive blood culture may be primary or secondary In typhoid fever for example the bacteremia occurs early in the disease with later localization of the organism in the lymphoid structures By contrast most staphylococcemias are secondary or complicating disturbances that ensue when a local abscess involves the wall of a vein and bacteria are introduced into the blood stream Primary bacteremias require systemic treatment but the secondary invasions additionally involve a search for the feeding focus and surgical intervention wherever feasible

A *pyemia* is a special type of bacteremia in which local purulent processes are produced as metastatic infections The condition of *septicemia* is of greatest gravity since it implies that the blood culture is positive and bacterial toxins are simultaneously circulating as in puerperal sepsis Septicemias require intensive local and systemic antibacterial and antitoxic treatment often combined with surgery

THE MANAGEMENT OF INFECTION BY THE PRACTITIONER

For the practitioner there is no greater challenge in clinical medicine than the management of the infectious state as it exists in his individual patient The importance of specific treatment makes it imperative that the diagnosis be established with the greatest accuracy by bacteriological and immunological methods Meanwhile without loss of valuable time an effort must be made to destroy the invading micro organism outside of the body on the skin and in accessible body orifices

Once the definitive bacteriological diagnosis has been established the practitioner *has a manifold responsibility to community and patient He* assists with public health measures to prevent dissemination of the infection In cooperation with the bacteriologist he determines the indications for examination It is his responsibility to decide whether to perform bacteriological or immunological tests If spreads and cultures are required he must collect the specimen under optimum conditions and preserve it before and during transfer to the laboratory His presumptive clinical diagnosis assists in settling technical problems such as the optimum media to be used Without his interpretation the laboratory report may be misleading He must decide whether an organism obtained from a throat culture is related to the disease process whether a typhoid agglutination has signifi

cance in the interpretation of a febrile illness whether the search for tubercle bacilli in sputum or spinal fluid must be repeated

While all of these problems are in a state of flux he does not neglect his patient He prescribes and administers specific chemotherapeutic and immunotherapeutic modalities he conducts palliative and symptomatic therapy in the best tradition of the union of the arts and sciences of medicine

CLINICAL DIAGNOSIS

The clinical diagnosis of an infection is based on considerations of epidemiology immunology localizing phenomena the results of therapeutic tests and the character of the temperature curve From this information the practitioner is often able to make a sufficiently accurate diagnosis to indicate the required laboratory investigations and initiate anti infective therapy

Epidemiology—In the analysis of a clinical infection it is a wise discipline to give first consideration to the prevailing disorder During the winter months in America the syndrome of fever general malaise and muscle aches suggests *grippe* whereas identical complaints in a mosquito infested island in the Pacific would arouse suspicion of *malaria* During the prolonged incubation period of *whooping cough* there is no better clue to the correct diagnosis than the history of contact in classroom or school Suffused eyes and nose in the midst of a *measles* epidemic are regarded as prodromes of the exanthem until proven otherwise The ailing child in a household where there is known *poliomyelitis* should be suspected of suffering from a subclinical or abortive attack of infantile paralysis with or without weakness of muscle groups

Immunology—The diagnosis of an infection is sometimes assisted by the immunological history We are inclined to dismiss from diagnostic consideration those infections which patients have already had and which are known to produce a lasting *acquired immunity* (p 76) We have not in our own experience seen second attacks of *measles scarlet fever* or *whooping cough* for example Alleged second attacks of measles and scarlet fever are most often rubella infectious mononucleosis drug rashes or secondary syphilis so called second attacks of pertussis we have found to be manifestations of lingual tonsillitis or intrathoracic disease

The practitioner may place great reliance upon the efficacy of *artificial immunization* (pp 76–87) He may rest fairly well satisfied in his assurance that quite complete protection is afforded by *diphtheria* and *typhoid* prophylaxis and should consider other possibilities before concluding that the presenting infection constitutes a failure of preventive medicine

Localizing Phenomena—The diagnosis of the infectious state is assisted by an appraisal of the localizing phenomena The presence of an eruption or associated respiratory enteric meningeal encephalitic urinary respiratory genital or hemic disturbance narrows the search within well defined limitations which are discussed elsewhere in greater detail (p 172)

Therapeutic Tests—There are times when the practitioner is compelled to perform a therapeutic test In these situations he should make an attempt to collect specimens for laboratory examinations before proceeding with probatory specific treatment In previous eras therapeutic testing was limited to the prescription of *quinine* in a suspected malaria of *salicylates*

in a rheumatic fever and of *arsenic* in suspected syphilis With the introduction of *sulfonamides* and *antibiotic* substances there are many situations in which the practitioner and his patient cannot or will not await the appearance of definitive laboratory reports and it is necessary to proceed immediately with the administration of anti infective remedies The diagnosis is then made in retrospect from the clinical response or the belated laboratory report

Temperature Curve —The appearance of the temperature curve has some diagnostic value Recurrent chills and fever with intervals of relative comfort characterize classical *malaria* afebrile episodes interspersed between febrile bouts are noted in the *relapsing fevers* and *brucellosis* of the Malta fever variety the Brill type of *typhus fever* quite consistently reveals a sharp crisis on the tenth eleventh or twelfth days unmodified *lobar pneumonia* in the period that preceded chemotherapy often terminated on the fifth sixth or seventh day by a dramatic temperature fall of 5 to 6 degrees

DIAGNOSTIC BACTERIOLOGY AND IMMUNOLOGY

The practitioner seeks to establish the identity of the invaders by the definitive methods of bacteriology and immunology Many of the microscopic methods can be conducted in the office laboratory Skin tests are performed with allergens purchased from reliable pharmaceutical manufacturers and some of the gross agglutination reactions can be observed by the use of simple testing sets More elaborate bacteriologic serologic and animal inoculation phenomena are the province of the experienced laboratory worker

MORPHOLOGICAL DIAGNOSIS BY DIRECT SMEAR

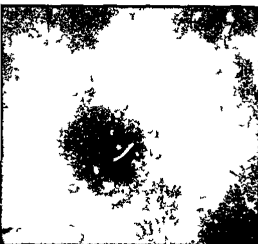
Direct smears and spreads made from culture media may be exceedingly useful in suggesting the exact nature of the invading organism Examinations are made by direct microscopy by darkfield examination or by the use of stains

Microscopic Examination of Unstained Material —In fungus infections scales hairs pus and sputum are examined directly with the higher powers of the microscope For the most part only the genera of fungi can be recognized by this method (p 485) For subdivision to species cultural methods are necessary

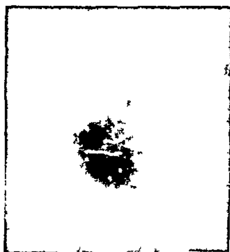
Darkfield Microscopy —Darkfield microscopy is a valuable procedure for the demonstration of spirochetes (p 329) The darkfield condenser has a central dark stop which prevents any direct light rays from entering the objective The specimen appears as a self luminous body on a nearly black background In performing the examination in suspected primary syphilis exudate is collected from a chancre or moist papule placed on a clean slide and covered with a glass coverslip A drop of cedar oil is placed between the darkfield condenser and the slide The slide is examined with the high dry or oil immersion lens If the latter is used a funnel light stop is required and the drop of cedar oil is placed on the coverslip For ordinary darkfield diagnostic work as in the demonstration of *Treponema pallidum* the high dry objective is preferable to the oil immersion lens it gives a larger field and a greater depth of focus the tendency for treponemas to dive in and out of focus is diminished and no funnel stop is necessary

The commonest reason for difficulty with darkfield technic is improper lighting A powerful source of parallel light rays is essential Bright sunlight and artificial light with a parallelizing system are the best sources To ob tain good results the following rules should be carefully followed

1 Use clean slides and coverslips of correct thickness (indicated on most condensers)


A


B


C


D

Fig 7—Darkfield microscopy of spirochetes (Collection of Dr Noguchi) *A Treponema microdentium* from the mouth *B Borrelia refringens* from culture *C Treponema genitalis* from smegma *D Treponema pallidum* from chancre

2 Center the darkfield condenser carefully
3 Clean the top of the condenser thoroughly
4 Remove air bubbles from the oil between condenser and slide
5 Make as thin a preparation as possible and avoid the presence of ex cessive amounts of blood
6 Consider the illumination adequate when the serum colloids are seen as moving points of bright light

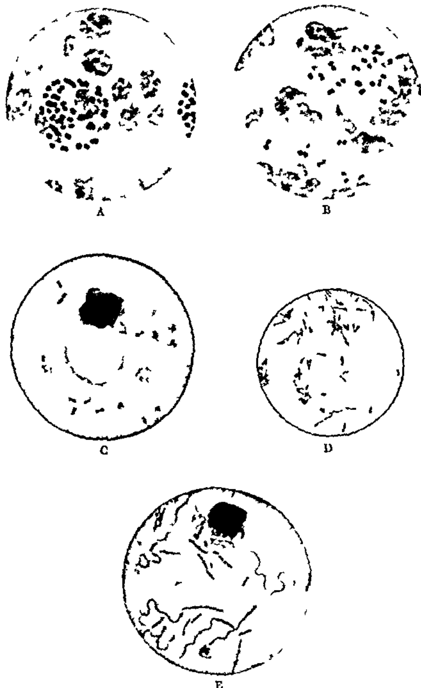


Fig 8.—Direct smears of pathogenic micro-organisms *A* Gonococci from urethral pus (Nowak) *B* Meningococci from cerebrospinal fluid (Nowak) *C* Pneumococci from sputum (Kolle and Wassermann) *D* *Corynebacterium diphtheriae* from exudate (Park) *E* Vincent organisms (Jordan and Burrows)

On darkfield examination the *Treponema pallidum* is seen as a slender delicate organism 10–12 microns in length having 6 to 18 sharp uniform rigid spiral curves the ends are pointed and the types of movement include rotation on the long axis flexion of the entire body and forward and back

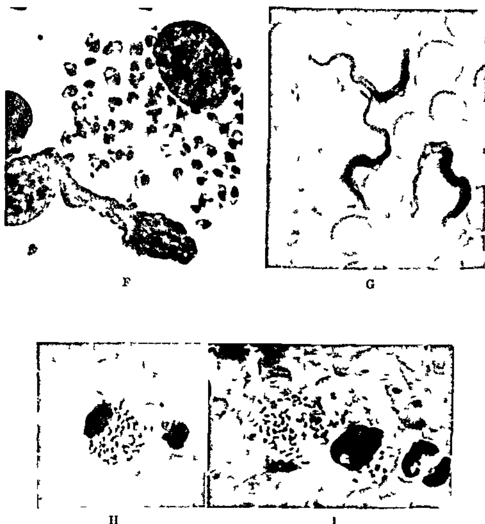


Fig 9—Direct smears of pathogenic micro-organisms (Man of Trop Med) *F Leishmania donovani* from spleen *G Trypanosoma gambiense* in blood *H* Donovan bodies from lesion of granuloma inguinale I Biopsy of lesion Donovan bodies in large mononuclear phagocytic cell (Courtesy of Dr Donald C A Butts)

ward progression The *T pallidum* is distinguished from *Borrelia refringens* a harmless saprophyte of the mouth and genital mucous membranes by the latter s fewer and shallower spirals the *leptospira* is longer than the treponema possesses fewer spirals has hook shaped extremities and peculiar

lashing movements mucocutaneous spirochetes as found in the various forms of *fusospirochetosis* may be difficult to identify on darkfield examination alone but they stain with carbolfuchsin or methylene blue (p 52)

Stained Smears—The examination by the practitioner of the stained smear is of greater utility than direct or darkfield microscopy Each of the latter procedures requires particular skill and training but the stained smear can be preserved re examined at leisure and sent to the expert for confirmation

Solutions—The material listed in Table 3 is required for staining

Table 3—Saturated Alcoholic Solutions for Stock Use

	Dye	Alcohol 9 Per Cent
Methylene blue	1 48	100 cc
Safranin	5 41	100 cc
Basic fuchsin	8 16	100 cc
Crystal violet	13 87	100 cc

The saturated alcoholic solutions listed in Table 4 are used to prepare the stains for office use

Table 4—Laboratory Solutions for Office Use

	Saturated Alcoholic Solution	Diluent
Methylene blue	5 cc	9 cc of distilled water
Loeffler methylene blue	30 cc	70 cc of distilled water containing 0 07 cc of 10 per cent KOH
Safranin	10 cc	90 cc of distilled water
Carbolfuchsin (Ziehl Neelsen)	10 cc (Basic)	85 5 cc of distilled water and 4 5 cc of phenol
Dilute carbolfuchsin	10 c (Ziehl Neelsen)	90 cc of distilled water
Gram s crystal violet	20 cc	80 cc of 1 per cent aqueous ammonium oxalate
Gram s iodine		Iodine 1 gm potassium iodide 2 gm water 300 cc
Acid alcohol		Hydrochloric acid 3 cc ethyl alcohol (95 per cent) 97 cc
Copper sulfate		*Copper sulfate* 0 gm water to 100 cc
Ethyl alcohol (9 per cent)		

TABLE 5 —MORPHOLOGICAL DIAGNOSIS BY DIRECT SMEAR

Those diseases indicated by italic type may be diagnosed with assurance by the appearance of the direct smear In all other circumstances confirmation is required from some other type of laboratory procedure such as culture serologic reaction or skin test

	Material for Examination	Method of Examination	Typical Organisms
Amebiasis	Stool pus	Direct	Endamoeba histolytica (p 593)
Anthrax	Pus	Gram spore	Gram positive bacillus with square-cut ends and central spore culture
Balantidiasis	Stool	Direct	Protozoa (p 1893)
Chancroid	Exudate from lesion or bubo	Gram	Gram negative bacillus (small) in chains skin test
Cholera	Stool	Gram	Gram negative comma shaped vibrio culture
Diphtheria	Exudate	Gram Loeffler	Slender gram positive bacillus with polar bodies culture
Filariasis	Blood	Darkfield Wright stain	Worm like microfilariae
Frambesia	Exudate	Darkfield	Spirochetes (p 351)
Friedlander infection	Sputum pus	Gram	Short plump gram negative encapsulated bacillus *culture*
Fusospirochetosis	Exudate sputum	Carbolfuchsin Gram	Long gram negative bacillus thick in middle and tapering towards ends long spirochetes with shallow irregular curves (p 355)
Gas gangrene	Exudate	Gram	Gram positive spore-bearing bacillus
Giardiasis	Stool	Direct	Protozoa (p 506)
Glanders	Pus	Gram	Gram negative slender bacillus with polar body culture
Gonorrhea	Pus blood	Gram	Gram negative intracellular biscuit shaped diplococcus culture
Granuloma inguinale	Exudate	Wright	Donovan bodies (p 475)
Helminthiasis	Stool urine	Direct	Ova or parasites (p 1893)
Infectious jaundice	Blood urine spinal fluid	Darkfield	Tightly coiled spirochete with hooked ends (p 360)
Infectious mononucleosis	Blood	Wright	Mononuclear cells in excess of 6 per cent serology

TABLE 5 —Cont ued

	Material for Examination	Method of Examination	Typical Organisms
Influen a	Spinal fluid	Gram	Gram negative pleomorphic bacillus culture
Lei hmaniasis	Spleen or marrow punc t ire	Wright	Leishman Donovan bod es (p 48)
Lepro y	Nasal scrapings skin biop y	Carbolfu hsin	Sl nd r straight bacilli oc curring in packets acid fast
Malaria	Blood	Wright	Plasmodia in red cells (p 507)
Me jo o c s i fect on	Spi nal fluid skin pu c ture	Gram	Gram negative intracellular d plococcus culture
Myc s	Scrapings sputum bi opsy	Direct	Fungi (p 489) culture
Pi ita	Exudate	Da kfiel l	Spi ochetes (p 5 3)
Plague	Pus of bul o sputum	Gram	Short thick pleomorphic gram negative bacilli with bipolar staining culture
P uno occus i fections	Sp nal flui l sputum	Gram cap ule	Large lancet shaped gram po itive cocci in pairs cul ture mouse inoculation
R lapsi g f ve	Blood	Wright	Sp rochet s with at out 5 larg spirals (p 5 7)
Staphylococcus infec ti ns	Pus spinal flui l	Gram	Gram po tive cocci in clus ters culture
Streptococcu i fections	Pus spinal fluid	Gram	Gram positiv cocci in short or long chains culture
Syphilis	Exudate or aspirate from node	Darkfield	D licate spirochetes with 6–18 sharp igid spirals s rology
Tetanus	Exu late	Gram spo e	Gram positive bacillus with drum tick spore culture
Tri hin sis	Mu le biopsy	Stain	Trichinellae (p 5 9)
Tr hom n s	Vaginal secretion	Direct	*Tri homonas vagin l s* (p 2598)
Trypanosom asis	Blood	Darkfield Wright	Tryp nosomes (p 531)
Tul ulosis	Exud te sputum urine spinal fluid pus	Carbolfuchsin	Acid fast slen ler bacillus seen also by fluorescence
Tularemia	Exud te	Gram	Small gram negative b c l lus animal inoculation

Technic of Staining—The technic of staining the smears is carried out in the following manner after fixing with heat or methyl alcohol

THE SIMPLE STAIN

1 Flood the slide with methylene blue for 2 to 5 minutes
2 Wash with water blot and dry

DILUTE CARBOLFUCHSIN

1 Flood the slide with dilute carbolfuchsin for 2 to 5 minutes
2 Wash with water blot and dry

GRAM STAIN

1 Flood the slide with the Gram crystal violet stain
2 After 1 to 2 minutes pour off excess and cover with Gram s iodine solution for 1 minute
3 Wash in water and decolorize with 95 per cent alcohol until no further traces of the violet can be detected in the wash water
4 Wash thoroughly again in water
5 Counter stain with aqueous Safranin

Note If difficulties are encountered purchase ready made Gram stain from a reliable manufacturer

ACID FAST STAIN (ZIEHL-NEELSEN)

1 Flood slide with carbolfuchsin (Ziehl Neelsen)
2 Heat gently with a free flame until steam appears on the surface
3 Continue the steaming for 5 minutes
4 Wash with water and decolorize with acid alcohol until only a faint pink remains and no further pink stain is visible in the wash water
5 Wash again with water
6 Counter stain with Loeffler s alkaline methylene blue for 1 minute

CAPSULE STAIN (HISS)

1 Flood the slide with Gram crystal violet or carbolfuchsin
2 Heat until steam appears and keep steaming for 1 to 2 minutes
3 Wash off the stain with 20 per cent aqueous copper sulfate
4 Blot dry but do not wash examine under a coverslip

SPORE STAIN

1 Apply carbolfuchsin as in Ziehl Neelsen method
2 Wash in hot tap-water
3 Rinse rapidly in 95 per cent alcohol
4 Apply Loeffler s methylene blue for 2 to 5 minutes
5 Rinse in tap-water blot and dry

BACTERIOLOGICAL CULTURES

Unless he has had unusual training the practitioner should refer bacteriological work to the expert The difficulties inherent in these studies include preparation of media and the provisions necessary for disposal of virulent cultures Many communities require licensing of bacteriology laboratories for public health protection For assistance in bacteriologic investigation the practitioner may call upon local state or Federal authorities if private facilities are not available

Collecting the Specimen—In most communities it is the physician s duty to take the culture transport it to the laboratory and offer a presumptive diagnosis for the guidance of the bacteriologist It is usually good

practice when facilities permit to discuss the clinical condition with the technical consultant so that the specimen may be obtained in a manner satisfactory to the laboratory specialist

Under almost every circumstance the superficial surface is cleansed to wipe away contaminants so that the actual culture is obtained from the depths of the wound *Sputum specimens* are collected after the patient has washed the mouth and has been instructed in the manner of bringing up secretion from the depths of the bronchi *urine specimens* require catheterization *spinal fluid* and *blood* are drained under aseptic precautions

The specimen should be brought to the bacteriological laboratory with the greatest haste since thermolabile organisms such as the meningococcus and gonococcus may not survive exposure to room temperature for more than a few moments and contaminants may overgrow or obscure a pathogen and produce a misleading negative report

Choice of Medium—The presumptive clinical diagnosis is of importance to the bacteriologist who then decides the optimum method of plating and growing his organism When the latter has been isolated it has diagnostic importance but may be used also for the preparation of an autogenous vaccine (p 77)

Blood Cultures—The detection of a bacteremia is of important significance in the diagnosis prognosis and treatment of the infectious state Before collecting the blood specimen the practitioner should obtain the necessary media and apparatus from the bacteriological laboratory so that the blood is collected under optimum circumstances

Technic—In taking blood cultures the skin in the antecubital region of the arm should be painted with tincture of iodine (3½ per cent) over a wide area Subsequently the iodine may be partly removed with 70 per cent alcohol The needle and syringe are preferably sterilized by dry heat in an oven At least 5 cc of blood should be removed since the smaller the quantity of blood sampled the less likely it is to be positive After removing the needle the blood is injected into the flamed mouth of a flask containing 100 cc of sterile infusion broth and the cotton stopper is replaced Contamination is most likely to occur at this stage of the procedure Care should be taken to prevent the blood or broth from coming in contact with the cotton plug The flask should be brought immediately to the laboratory and incubated

The length of time necessary for organisms to be demonstrable in a blood culture varies with the bacteria and with the number of organisms originally present in the blood sample Most bacteria produce visible growth usually accompanied by darkening of the media when the flask is stirred up in twenty four to forty eight hours Some like *brucella* take ninety six or more hours Heavy bacteremias with pneumococci staphylococci or streptococci often can be recognized in twelve to eighteen hours No blood culture should be discarded as negative before at least five days incubation and in the case of *brucella* the culture should be incubated for three weeks

Interpretation—The following organisms when isolated from blood cultures are generally etiologic agents of disease and in most instances bacteremia with these organisms is of grave prognostic significance *Staphylococcus aureus hemolytic* and *green producing streptococci pneu*

Technic of Staining—The technic of staining the smears is carried out in the following manner after fixing with heat or methyl alcohol

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Collecting the Specimen—In most communities it is the physician s duty to take the culture transport it to the laboratory and offer a presumptive diagnosis for the guidance of the bacteriologist It is usually good

TABLE 6—*Continued*

	Material	Media	Remarks
Tetanus	Exudate	Cooked meat media	Anaerobic
Tuberculosis	Sputum urine pus spinal fluid	Egg potato and glycerin media	Prolonged observation
Tularemia	Pus blood	Blood cystine agar	Virulent
Typhoid fever	Urine stool blood bile	Eo in methylene blue agar	Translucent colonies or pinkish colonies
Typhus fever	Blood skin l…on	Chick embryo or tissue culture	Virulent
Whooping cough	Cough plate sputum	Potato glycerin blood agar	Pearl like colonies

mococci meningococci gonococci E typhosa salmonellae brucella Fried lander bacilli P tularensis P pestis B anthracis and *H influenzae*

In the following bacterial diseases blood cultures rarely can be expected to be positive *diphtheria tetanus gas gangrene dysentery botulism cholera tuberculosis leprosy chancroid* and *pertussis* Blood cultures taken on ordinary media are always negative in virus diseases unless there is secondary bacterial septicemia (staphylococcus hemolytic streptococcus) They are likewise negative in spirochetal and protozoal diseases although these agents may be detected by darkfield examination or in stained blood smears

Significance of Blood Cultures—A positive blood culture is always of more significance than a negative one since the latter does not definitely rule out the possibility of septicemia In some infections (subacute bacterial endocarditis) septicemia is intermittent The first culture may be negative while subsequent cultures will be positive In general it is preferable to take cultures at the height of fever or on the rising curve of a febrile paroxysm

When *Staphylococcus albus green producing streptococci* and *colon bacilli* are grown from blood cultures clinical judgment is required to assess their significance These organisms are normal inhabitants of the skin and mucous membranes and may contaminate blood cultures that are improperly taken On the other hand all three bacteria are at times responsible for serious and often fatal septicemia sometimes with endocarditis Whenever there is doubt the wisest course it to take *repeated* blood cultures If they remain positive their significance can no longer be questioned

SEROLOGIC AND SKIN TESTS

The demonstration of immune bodies in the serum and skin has considerable diagnostic value The practitioner may perform skin tests with diagnostic allergen obtained from commercial laboratories or local state and Federal agencies also he may perform macroscopic agglutination tests in the enteric fevers and brucellosis For the rest however expert labora

TABLE 6.—CULTURE METHODS IN THE DIAGNOSIS OF INFECTION

	Material	Media	Remarks
Anthrax	Pus	Extract agar	Highly virulent
Botulism	Food	Extract agar	Anaerobic
Brucellosis	Blood, urine or pus	Chocolate blood agar	Increased tension of CO_2
Chancroid	Exudate or aspirate from bubo	Blood agar	Keep moist
Cholera	Stool	Peptone solution	pH 8 to 8.4
Colon infections	Urine or blood	Eosin methylene blue agar	Colonies with dark center and greenish metallic sheen; agglutinate
Diphtheria	Exudate	Enriched serum or tellurite agar	Black colonies
Dysentery (bacillary)	Stool	Eosin methylene blue agar	Colonies translucent, colorless or pink; agglutinate
Friedlander infections	Sputum, blood or pus	Eosin methylene blue agar	Slimy growth
Gas gangrene	Pus	Cooked meat media	Anaerobic
Glanders	Pus	Glycerin media	Colonies chocolate colored later
Gonorrhea	Pus, blood	Chocolate agar	Increased tension of CO
Influenza	Blood, spinal fluid	Blood or chocolate agar	Small transparent colonies
Meningococcus infections	Blood, spinal fluid	Blood or chocolate agar	Increased tension of CO_2
Mycoses	Scraping	Sabouraud media	Prolonged observation
Plague	Pus, sputum	Serum agar	Virulent
Pneumococcus infections	Blood, sputum, spinal fluid	Blood agar	pH 7.6 to 7.8; translucent colonies with greenish rim
Q fever	Blood	Agar slant tissue culture	Virulent
Rocky Mountain spotted fever	Blood	Tissue culture	Virulent
Salmonella infections	Stool	Eosin methylene blue or desoxycholate citrate sugar	Translucent colorless or pinkish colonies
Staphylococcus infections	Pus, blood, spinal fluid	Blood agar	White or golden colonies
Streptococcus infections	Pus, blood, spinal fluid	Blood agar	Green or hemolytic colonies

chief means of laboratory diagnosis The outstanding example is the *flocculation test* for syphilis elsewhere discussed (p 334)

Complement Fixation Test—The complement fixation test is probably the most widely used immunologic procedure in medical practice Blood for the complement fixation test is obtained as previously described for agglutination tests It is important to prevent hemolysis of the blood and to obtain clear serum free of bacterial contaminants as these may interfere with the proper performance of the test

TECHNIC—The principle on which the test depends is the fixation or binding of complement by a specific antigen antibody reaction using a hemolytic system as an indicator The patient s serum is heated to 56° C to inactivate naturally present complement It is then mixed in definite proportions with the antigen and a known amount of complement is added in the form of a previously titered fresh normal guinea pig serum If the antigen and antibody are specific (*i e* if the patient s serum contains specific antibodies for the antigen used) the two react and in so doing bind or inactivate the added complement The next step is a test to determine whether or not the complement has been bound To do this sheep cells and anti heep rabbit serum are needed The latter is prepared by immunizing

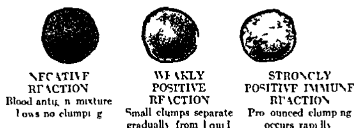


Fig 10—Pertussis agglutination test (Courtesy of Eli Lilly Co)

rabbits with sheep cells When sheep cells and antisheep rabbit serum (called *amboceptor*) are mixed they also bind complement and the sheep cells become hemolyzed Hemolysis will not occur in the absence of complement Therefore to the antigen antibody complement system described above sheep cells and amboceptor are added If the antigen and antibody are specific and have reacted the complement has been bound and the sheep cells do not hemolyze The tube shows a sediment of sheep cells and a supernatant layer of clear serum indicating a *positive test* On the other hand if the patient s serum does not contain specific antibody complement is not fixed but is left free to hemolyze the sheep cells The negative tube has no sediment and the fluid is uniformly stained with red coloring matter

INDICATIONS—Complement fixation tests may be done in amebiasis blastomycosis brucellosis chancroid cholera coccidioidomycosis echinococcus infestations equine encephalomyelitis foot and mouth disease glanders gonorrhea histoplasmosis infectious jaundice Japanese B encephalitis leishmaniasis lymphocytic choriomeningitis lymphopathia venereum malaria moniliasis mumps ornithosis whooping cough pneumonia psittacosis Q fever rat bite fever relapsing fever Rocky Mountain spotted fever Russian seasonal encephalitis St Louis encephalitis salmonella

tory assistance is required and the results must be considered in the light of clinical findings

Serologic Tests—For serologic tests the blood is collected in a clean dry test tube using a dry syringe and a sterile dry needle At least 10 cc are required for the test tube methods of agglutination but less is needed if the slide method is employed The blood does not have to be sterile but hemolysis must be prevented by avoidance of moisture

Indications—Agglutination reactions may be made in actinomycosis brucellosis cholera dysentery glanders infectious jaundice infectious mononucleosis leishmaniasis pertussis plague Q fever relapsing fever, Rocky Mountain spotted fever paratyphoid A and B sporotrichosis trench fever tsutsugamushi fever tuberculosis tularemia typhoid and typhus

Rapid Slide Agglutination Method (Office Laboratory)—The rapid slide agglutination method is simple and easily performed in the practitioner s laboratory All the necessary equipment including the antigens is available commercially The technic is generally regarded as reliable and comparable in accuracy to the older macroscopic tube method

The test is performed on a large glass plate which is marked off into compartments with a wax pencil With a special pipette a drop of the patient s serum is placed in each of a number of compartments 0 08 cc is delivered into the first space 0 04 into the next 0 02 into a third 0 01 cc into a fourth and 0 005 cc in the fifth Then with a special dropper supplied with commercial antigens 0 03 cc of antigen is placed in each compartment and mixed with the serum by the use of a toothpick These amounts of antigen and serum are so calculated that the final dilutions correspond to 1 20 1 40 1 80 1 160 and 1 320

The whole slide is rocked back and forth and examined for visible agglutination or clumping which occurs in a few minutes A good light is necessary but the reaction is generally obvious when positive The titers are recorded in terms of the dilutions according to the macroscopic method

Interpretation of Agglutination Tests—There are many pitfalls in the interpretation of agglutination tests which depend on a number of variables These include the time the blood was drawn in relation to the course of the disease the specificity and cross reactivity of the antigens used whether or not the patient had active infection or was a carrier the possibility of an anamnestic reaction the effect of previous vaccination the *persistence of agglutination for indefinite periods after illness and individual* variation in the ability to develop agglutinins

Agglutinins may be absent or present in insignificantly low titers even in the presence and throughout the course of an acute infection with the organism in question It is most difficult to define categorically the titers which may be considered significant In dysentery infections normal persons often have higher titers than sufferers from the disease

In general a *rise in titer* during the course of an illness is of great significance When cross reactions are encountered the titer for the true bacterial incitant rises whereas the titer for the cross reacting antigen tends to remain constant and at a lower level

Precipitin Tests—Blood for precipitin tests is obtained in the same manner as for agglutination tests The precipitin tests are simple and precise but unfortunately there are only a few instances where they are the

Table [illegible].—Serologic and Skin Tests in the Diagnosis of Infection

+ indicates tests of greatest importance

	Agglutinins	Precipitins	Complement Fixation	Neutralizing Bodies	Skin Tests
Actinomycosis	+ (1:300)	0	0	0	+
Amebiasis	0	+	+	0	0
Ascariasis	0	+	0	0	+
Blastomycosis	0	0	+	0	+
Brucellosis	+ (1:100)	0	+	0	+
Chancroid	0	0	+	0	+
Cholera	+ (1:10)	0	+	+	0
Coccidioidomycosis	0	+	+	0	+
Diphtheria	0	0	0	0	+
Dysentery (bacillary)	+ (1:60)	0	0	0	+
Echinococcus	0	+	+	0	+
Epidemic keratoconjunctivitis	0	0	0	+	0
Equine encephalomyelitis	0	0	+	+	0
Filariasis	0	0	0	0	+
Foot and mouth disease	0	0	+	+	0
Glanders	+ (1:100)	+	+	0	+
Gonococcus	0	+	+	0	+
Histoplasmosis	0	0	+	+	+
Infectious jaundice	+ (1:40)	0	+	0	0
Infectious mononucleosis	+ (sheep red cells)	0	0	0	0
Influenza A	0	0	+	+	0
Japanese B encephalitis	0	0	+	+	0
Leishmaniasis	+ (1:10)	+	+	0	+
Lymphocytic choriomeningitis	0	0	+	+	0
Lymphopathia venereum	0	0	+	+	+
Malaria	0	+	+	0	0

infections schistosomiasis sporotrichosis syphilis trichinosis trypanosomiasis tuberculosis typhoid typhus *yaws and yellow fever*

INTERPRETATIONS.—The complement fixation test offers many difficulties in interpretation The completely *negative* findings usually preclude

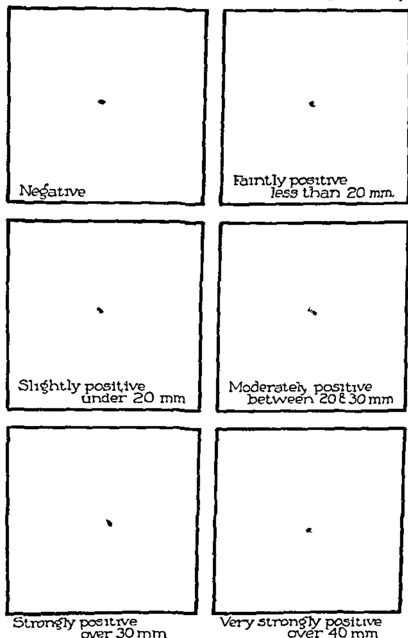


Fig 11—Positive and negative Dick reactions (From Dick and Dick *Scarlet Fever* Year Book Publishers Inc., Chicago Ill)

the presence of the disease after the first few weeks however notably in *syphilis* the complement fixation test may be negative while the infection is in its most florid phase thus offering completely misleading information

TABLE 7 —*Continued*

	Agglutinins	Precipitins	Complement Fixation	Neutralizing Bodies	Skin Tests
Typhoid	+ {over 1:80 with H over 1:80 with O}	0	+	0	0
Typhus	+ {Proteus OX19 in high OXK in 2nd wk}	0	+	0	+
Yaws	0	+	+	0	0
Yellow fever	0	+	+	+	0

Adapted from Kolmer J A and Tuft L Clinical Immunology Biotherapy and Chemotherapy Philadelphia W B Saunders Company 1941

The *positive test* indicates merely that the individual has suffered from the infection It does not mean necessarily that the presenting symptoms are related to the organism to which complement fixation has been demonstrated Using syphilis as an example again the Wassermann test may be positive while the patient is suffering from tuberculosis an upper respiratory infection or carcinomatosis The laboratory reports that the patient is a syphilitic but it does not necessarily imply that there is any relationship between the reported finding and the current complaints (p 337)

The *false positive* test is most misleading of all It is a transitory finding due to some intercurrent variable such as is exemplified by the false positive Wassermann in infectious mononucleosis malaria and leprosy

The Neutralizing Bodies —Demonstration of neutralizing bodies is of most value in the virus diseases Laboratory information is available in epidemic keratoconjunctivitis equine encephalomyelitis foot and mouth disease herpes simplex histoplasmosis influenza A Japanese B encephalitis lymphocytic choriomeningitis lymphopathia venereum mumps poliomyelitis Russian seasonal encephalitis St Louis encephalitis and yellow fever

Demonstration of the neutralizing bodies is a most exacting technic and quite beyond the province of all but specially trained workers The reaction is highly specific and is of most value in the recognition of sub clinical and abortive infections

Skin Tests —Skin tests are increasingly useful in a large number of diseases including tuberculosis brucellosis lymphopathia venereum chancroid the mycoses trichinosis scarlet fever tularemia and leprosy

The Positive Test —The positive skin test is not proof that the present illness of the patient is related to the immunologic findings The specific reaction may indicate a process that is walled off latent or even entirely healed The interpretation of the finding requires correlation with the clinical facts

The Negative Test —Negative tests are often of greater diagnostic help than those that are positive It is only under rare circumstances that the negative test is misleading it may be performed too soon after the onset

TABLE 7—*Continued*

	Agglutinins	Precipitins	Complement Fixation	Neutralizin Bodies	Skin Tests
Meningococcus	+ (1:10)	0	0	0	+
Moniliasis	+ (1:10)	0	+	0	0
Mumps	0	0	+	0	0
Ornithosis	0	0	+	0	0
Pertussis	+ (1:200)	0	+	0	0
Plague	+ (1:10)	+	0	0	0
Pneumococcus	+ (1:10)	+	+	0	+
Poliomyelitis	0	0	0	+	0
Psittacosis	0	0	+	+	0
Q fever	+ {OX19 neg but R burneti +}	0	+	0	0
Rat bite fever	0	0	+	0	0
Relapsing fever	+ (1:40)	0	+	0	0
Rocky Mountain spotted fever	+ as Typhus	0	+	0	0
Russian seasonal encephalitis	0	0	+	+	0
St Louis encephalitis	0	0	+	+	0
Salmonellae	+ (1:20)	0	+	0	0
Scarlet fever (streptococcus)	+	+	0	0	+
Schistosomiasis	0	+	+	0	+
Sporotrichosis	+ (1:200)	0	+	0	+
Syphilis	0	+	+	0	0
Trench fever	+	0	0	0	0
Trichinosis	0	+	+	0	+
Trichophytosis	0	0	0	0	+
Tsutsugamushi fever	+ {OX19 neg OXK pos}	0		0	0
Trypanosomiasis	0	+	+	+	0
Tuberculosis	+ (1:10)	+	+	0	+
Tularemia	+ {over 1:80 with negative Brucella}	0	0	0	+

TABLE 7 —*Continued*

	Agglutinins	Precipitins	Complement Fixation	Neutralizing Bodies	Skin Tests
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The Negative Test —Negative tests are often of greater diagnostic help than those that are positive It is only under rare circumstances that the negative test is misleading it may be performed too soon after the onset

TABLE 8—ANIMAL INOCULATION IN THE DIAGNOSIS OF INFECTION

	Animal	Method of Injection	Remarks
Anthrax	Mouse guinea pig	Subcutaneous	Bacilli in blood and spleen within 1 to 2 days
Botulism	Mouse guinea pig	Subcutaneous	Controls protected by antitoxin survive but others die of respiratory or cardiac failure
Brucellosis	Guinea pig (male)	Subcutaneous	Caseous nodules in spleen liver and lymph nodes in 4-12 weeks
Cholera	Guinea pig	Intraperitoneal	Peritonitis in 1-2 days bacteriolysis in 30 minutes in immunized animal (Pfeiffer reaction)
Diphtheria	Guinea pig	Subcutaneous	Controls protected by antitoxin but others develop local edema and hemorrhage into adrenals
Encephalitis	Mice	Intracerebral	Encephalitis
Gas gangrene	Guinea pig pigeon	Intramuscular	Local dissolution of muscles with crepitation and gas formation controls protected by antitoxin
Glanders	Guinea pig (male)	Intraperitoneal	Orchitis in 1-2 days miliary granulomas
Infectious jaundice	Guinea pig mouse	Intraperitoneal Subcutaneous	Leptospira in blood in 7-12 days hemorrhage and jaundice
Lymphocytic choriomeningitis	Guinea pig	Subcutaneous	Pneumonia focal hepatitis and death in 9 to 16 days
Plague	Mouse guinea pig	Subcutaneous	Hemorrhagic lymphadenitis and death in 2-5 days
Pneumococcus	Mouse	Intraperitoneal	Peritonitis with specific organism in 3-6 hours
Rabies	Dog	Intracerebral	Encephalitis with Negri bodies
Rat bite fever	Mouse rat guinea pig	Intraperitoneal	Fever and enlarged nodes and sepsis in 5-14 days
Rocky Mountain spotted fever	Guinea pig (male)	Intraperitoneal	Scrotal swelling only with virulent strains few organisms in tunica vaginalis
Q fever	Guinea pig (male)	Intraperitoneal	None
Smallpox	Rabbit	Eye	Keratitis with Guarnieri bodies
Staphylococcus food poisoning	Kittens	Intraperitoneal	Vomiting in 1-2 days
Tetanus	Guinea pig	Subcutaneous	Spastic paralysis in animals unprotected by antitoxin
Tsutsugamushi fever	Guinea pig (male)	Intraperitoneal	None

TABLE 8.—*Continued*

	Animal	Method of Injection	Remarks
Tuberculosis	Guinea pig	Subcutaneous	Caseous lesions in 6–8 weeks
Tularemia	Mouse guinea pig rabbit	Subcutaneous	Hemorrhagic lymphadenitis and caseation in 2 7 days
Typhus (epidemic)	Guinea pig (male)	Subcutaneous	Rickettsia localized within cytoplasm or in exudate of tunica vaginalis
Typhus (murine)	Guinea pig (male)	Intraperitoneal	Scrotal lesions rickettsia in tunica vaginalis

of the disease the skin may be anergic or the general condition of the patient may be so unsatisfactory that antibodies do not form Under other circumstances the negative test is a denial of the presence of the suspected invader

False Positive Tests.—Test allergins are complex proteins prone to give false positive reactions The non specific skin responses are generally seen during the course of the first twenty four hours and tend to disappear after twelve to thirty six hours By contrast the true positive reaction is of slower development it rarely appears before thirty six to forty eight hours and may persist for several days or weeks

ANIMAL INOCULATION

Bacteriologists are making increasing use of experimental animals as culture media for diagnostic information and to indicate the virulence of



Fig 12.—Diagnosis by animal inoculation (Simmons and Gentzkow Laboratory Methods of United States Army Lea & Febiger) *A* Scrotal swelling in murine typhus fever *B* Scrotal necrosis in Rocky Mountain spotted fever

the invading organism (Table 8) The practitioner should not try to perform this type of experimentation since the handling of the infected animal is a hazard and requires the resources of a fully equipped institute

TREATMENT OF THE INFECTIOUS STATES

The therapeutic program is aimed at the control and defeat of the organism which has invaded the tissues of the human host It combines measures to protect the public health meanwhile affording remedial therapy for the support and symptomatic comfort of the patient It includes the more spectacular specific chemotherapeutic immunotherapeutic and antibiotic assaults on the pathogen

Public Health Measures in the Communicable Diseases

In the management of the infectious state the practitioner has an obligation to the individual patient and a broader responsibility to the susceptible community The former discipline constitutes the practice of medicine whereas the latter is the province of public health or preventive medicine

In the interests of the public health it is the practitioner s duty to locate the source of the infection The bacterial invader may be of autogenous or heterogenous origin In the former instance as in invasion by a mouth pneumococcus the resistance of the patient has been lowered and the normal inhabitant of the mucous membrane now becomes a tissue invader of hostile character In the majority of instances the invading bacterium is of heterogenous origin and the disease is referred to as communicable

Definition of Terms—An infectious disease results from the invasion of the tissues of the host by a micro organism or parasite The term com*municable implies that the invading organism is transferred from indi*vidual to individual The contagious or catching diseases are transferred from host to host without an intermediary A vector disease is one that requires the intermediation of another living organism Thus malaria under ordinary circumstances is not transmitted from host to host The mosquito functions as the vector or intermediary The term vector is commonly restricted to a living intermediary and would not include for example the drinking of polluted water in the transmission of typhoid fever

In tracing the source of infection the first recognized or known victim is the primary case ' Individuals who derive their disease from the primary source are known as secondary cases An epidemic refers to an unusual prevalence of a particular disease in a given time and place without reference to the method of the spread of the infection A pandemic is the world wide occurrence of an infectious disease or an unusual prevalence during a relatively short time Thus in a town of 5 000 the appearance in the period of a month of a hundred or more pneumococcus pneumonias might justly be termed an epidemic The waves of influenza in 1889 and 1918–1919 exemplify the recurrent pandemic

Endemic disease refers to the usual prevalence of a communicable disease among a limited population Thus in any large city pneumococcus pneumonia is endemic throughout the Fall and Winter months An epizootic disease is an infection of lower animals analogous to epidemic in the human

Sources of Infection —The elucidation of the source of infection is the problem of the epidemiologist to whom the practitioner owes complete cooperation The sources of infection may be

1 The typical case such as the patient
2 The atypical or subclinical case that is abortive or missed often seen in other members of the family household or class
3 The carrier in a stage of incubation
4 The healthy chronic carrier (typhoid fever)
5 The convalescent carrier (dysentery meningitis)
6 The latent state of chronic disease such as syphilis and tuberculosis
7 The carrier or infected state in lower animals (tuberculosis in cattle brucellosis in goats)
8 Contaminated milk food or water as in typhoid and dysentery
9 Inanimate substances such as urine stool saliva sputum laboratory or surgical materials sweat epithelial scales pus or blood
10 Insect vectors

Methods of Infection —The practitioner s responsibility is the prevention of secondary cases originating from his individual patient He is required to notify the public health authorities so that these officials may trace the source of infection responsible for the illness of the particular patient in question Local state and Federal agencies are available for notification assistance in diagnosis isolation and treatment

Individual prophylaxis relative to the community varies with the bacterial source Thus with syphilis or skin infections such as erysipelas the danger of contagion is through contact In the airborne or droplet infection (tuberculosis upper respiratory infection and pneumonia) the danger of transmission is via the nose and throat In the enteric diseases such as typhoid fever both urine and stool contain the living organism The main problems concern the disposal of excreta and the prevention of soiling of hands bed linen instruments and utensils

In the vector diseases the patient is not a menace but the living intermediary such as the mosquito in malaria must be destroyed

With infestation soil contamination may occur The enteric organism may be transferred by food handling to raw and uncooked edibles

Measures of Public Health Control —The measures employed for public health control are individual or general For the infected patient aseptic technic is employed by the nurses and attendants This includes the use of gowns masks and gloves and the destruction or sterilization of soiled material and excreta On a wider scale recognized or suspected cases of infection are isolated and contacts are quarantined by public health agencies

The Control and Immunization of Contacts —The control of contacts varies in the different diseases The problem is particularly difficult in susceptible children exposed to an infected child in school or play groups In general the contact should be examined bacteriologically where possible for assurance that the subject is not a healthy carrier or in an incubation or subclinical period Susceptible contacts where possible should be immunized or receive prophylactic chemotherapy

TABLE 9.—CASE, CONTACT, AND DWELLING STATUS OF REPORTABLE INFECTIOUS DISEASES

*Detroit 1940**

Disease and Incubation Period	Status of Dwelling	Status of Case	Status of Contact in Home†
Chickenpox (14–21 days)	Warning placard	Isolation until skin entirely clear	Susceptible child contacts must be excluded from school from 12th to 21st day after exposure
Common cold (12–72 hours)	No placard	Isolation desirable	No quarantine
Diphtheria (1–10 days, average 2–5 days)	Quarantine placard	Isolation (minimum 11 days)	Quarantine; wage earners may be permitted to enter and leave premises if they have no contact with the patient, with children, or with food for public consumption
Dysentery, amebic (? days–several weeks)	No placard	Isolation desirable	No quarantine
Dysentery, bacillary (2–7 days)	No placard	Isolation desirable	No quarantine; chemotherapy with sulfonamides (p. 247)
Encephalitis (4–21 days)	No placard	Isolation for one week after onset	No quarantine
Erysipelas (2–7 days)	No placard	Isolation until recovery	No quarantine
Food infection (1–24 hours after ingestion of food)	No placard	No isolation	No quarantine
German measles (14–21 days, average 17 days)	No placard	Isolation (minimum 7 days)	No quarantine
Impetigo (2–5 days)	No placard	Exclusion from school	No quarantine
Influenza (1–3 days)	No placard	Isolation until recovery	No quarantine
Leprosy (few months to several years)	No placard	Isolation in leprosarium	No quarantine
Malaria (about 14 days)	No placard	Protect from bites of mosquitoes	No quarantine
Measles (8–12 days, average 10 days)	Warning placard	Isolation (minimum 7 days)	Susceptible children must be excluded from school for 14 days after exposure; prophylactic immunotherapy with modifier (p. 416)
Meningococcic meningitis (2–10 days, average 5 days)	Quarantine placard	Isolation (minimum 14 days)	Quarantine minimum period of 14 days for contacts living in the home except wage earners who may enter and leave the premises if they have no contact with patient, with children, or with food for public consumption; prophylactic chemotherapy with sulfonamide (p. 88)
Mumps (14–21 days, average 18 days)	No placard	Isolation until recovery	No quarantine
Pneumococcic pneumonia (1–3 days, not well determined)	No placard	Isolation desirable	No quarantine
Poliomyelitis (4–14 days)	Quarantine placard	Isolation minimum 14 days from onset	Quarantine minimum period of 7 days except wage earners who may enter and leave the premises if they have no contact with patient, with children, or with food for public consumption

Psittacosis (6 14 days)	*No placard*	Isolation of patient during acute clinical stage	No quarantine of human beings Quarantine if psittacine birds in home
Rabies (2 weeks to 6 months)	No placard	Patient should be under adequate *medical supervision*	No quarantine
Rocky Mountain spotted fever (3–10 days)	No placard	Isolation not required	No quarantine
Scarlet fever (1–10 days average ~5 days)	Quarantine placard	Isolation minimum 14–21 days and until recovery	Quarantine minimum period 14–21 days wage earners may enter and leave the premises if they have no contact with patient with children or with food for public consumption prophylactic chemotherapy with sulfonamide (p 181)
Smallpox (8–12 days average 10 days)	Quarantine placard	Isolation	Quarantine for 21 days from last exposure unless successfully vaccinated
Streptococcus (septic) sore throat (1–3 days)	No placard	Isolation until recovery	No quarantine prophylactic chemotherapy with sulfonamide (p 167)
Syphilis (variable)	No placard	Isolation for uncooperative persons	No quarantine
Tetanus (4 days to 3 weeks)	No placard	Isolation not required	No quarantine
Trichinosis (4–10 days variable)	No placard	Isolation not required	No quarantine
Tuberculosis (variable)	Placarding isolation or quarantine not generally used in administrative contro		
Tularemia (1–10 days average 3 days)	No placard	Isolation not required	No quarantine
Typhoid fever (3–28 days average 7–14 days)	No placard	Isolation until 3 successive negative cultures obtained at 24 hour intervals	No quarantine
Typhus fever (5–20 days average 12 days)	No placard	Isolation in a vermin free room	No quarantine unless human beings have lice
Undulant fever (6–30 days variable)	No placard	Isolation not required	No quarantine
Venereal diseases (other than syphilis)	Placarding isolation or quarantine not generally used in administrative control		
Vincent s angina (variable)	No placard	Exclusion from school	No quarantine
Whooping cough (7–14 days average 10 days)	Warning placard	Isolation (minimum 3 weeks)	Quarantine until patient released from isolation for children who are not protected or have not had the disease

* Adapted from Top F H et al Handbook of Communicable Diseases St Louis C V Mosby Company 1941

† In all instances where quarantine restrictions are necessary exposed children may be released to live elsewhere provided they are excluded from school and public gatherings for a period of seven days from the last possible contact with the patient (poliomyelitis—children under 16 years scarlet fever) one or more *negative cultures obtained (diphtheria meningococcic meningitis) excluded from school for 14 days* unless inoculated against the disease (whooping cough) and strict quarantine for 21 days if not successfully vaccinated (smallpox)

TABLE 9.—CASE CONTACT AND DWELLING STATUS OF REPORTABLE INFECTIOUS DISEASES

Detroit 1940

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Common cold (12–72 hours)	No placard	Isolation desirable	No quarantine
Diphtheria (1–10 days average 2–5 days)	Quarantine placard	Isolation (minimum 11 days)	Quarantine wage earners may be permitted to enter and leave premises if they have no contact with the patient with children or with food for public consumption
Dysentery amebic (2 days–several weeks)	No placard	Isolation desirable	No quarantine
Dysentery bacillary (2 7 days)	No placard	Isolation desirable	No quarantine chemotherapy with sulfonamides (p 247)
Encephalitis (4–21 days)	No placard	Isolation for one week after onset	No quarantine
Erysipelas (2 7 days)	No placard	Isolation until recovery	No quarantine
Food infection (1–24 hours after ingestion of food)	No placard	No isolation	No quarantine
German measles (14–21 days average 17 days)	No placard	Isolation (minimum 7 days)	No quarantine
Impetigo (2–5 days)	No placard	Exclusion from school	No quarantine
Influenza (1–3 days)	No placard	Isolation until recovery	No quarantine
Leprosy (few months to several years)	No placard	Isolation in leprosarium	No quarantine
Malaria (about 14 days)	No placard	Protect from bites of mosquitoes	No quarantine
Measles (8 12 days average 10 days)	Warning placard	Isolation (minimum 7 days)	Susceptible children must be excluded from school for 14 days after exposure prophylactic immunotherapy with modifier (p 416)
Meningococcic meningitis (2–10 days average 5 days)	Quarantine placard	Isolation (minimum 14 days)	Quarantine minimum period of 14 days for contacts living in the home except wage earners who may enter and leave the premises if they have no contact with patient with children or with food for public consumption prophylactic chemotherapy with sulfonamide (p 88)
Mumps (14 21 days average 18 days)	No placard	Isolation until recovery	No quarantine
Pneumococcic pneumonia (1–3 days not well determined)	No placard	Isolation desirable	No quarantine
Poliomyelitis (4–14 days)	Quarantine placard	Isolation minimum 14 days from onset	Quarantine minimum period of 7 days except wage earners who may enter and leave the premises if they have no contact with patient with children or with food for public consumption

Clinical Manifestations—The presence of an acute coronary insufficiency is suspected in the presence of the undernoted associated conditions

1 There must be an initial episode of an acute nature which (*1*) demands an increased volume output from the heart, (*2*) impedes an adequate venous return to the heart (peripheral circulatory failure) or (*3*) interferes with the oxygen carrying capacity of the circulating fluid (hemorrhage)

2 In the course of this extracardiac disturbance the practitioner notes a *sudden drop in blood pressure* or the acute onset of manifestations of *circulatory deficiency* (p 920) At times, the objective appearances are supplemented by the subjective complaint of *angina pectoris* (p 890)

3 Transient R T segment depressions are demonstrable in one or several leads The T waves are usually inverted at the same time but return to normal in one or two weeks **(ECG 11, 12, 13, 14, 64)**

Differential Diagnosis—The immediate diagnostic problem in the face of an acute coronary insufficiency is the differentiation between this condition and an *acute coronary closure* (p 993) or the coexistence of both conditions The presence of vascular occlusion is undeniable if the patient exhibits elevation of temperature leukocytosis, increase of the sedimentation time and the later development of a pericardial friction rub Increasing changes in serial electrocardiographic tracings leave no doubt as to the progression from a purely functional to a morphological entity

Prognosis—The differentiation between acute coronary insufficiency and a vessel closure has both prognostic and therapeutic importance There is every reason to anticipate complete recovery in an acute coronary insufficiency if the fundamental provocative mechanism can be corrected before the establishment of pathologic change in the myocardium The long range prospect in a coronary artery occlusion is considerably less promising with the almost certain anticipation of increasing circulatory difficulties

Treatment—The importance of recognizing the clinical entity of acute coronary insufficiency resides in the therapeutic implications Whereas in a coronary artery occlusion the practitioner seeks to obtain rest and quiet at any cost active therapy may be necessitated in an acute coronary insufficiency in order to prevent permanent damage to the myocardium

In either condition an opiate may be injected intravenously for immediate relief of discomfort and apprehension oxygen inhalations are given in high concentration and minimum demands are made upon the patient s physical and emotional resources

The active treatment of acute coronary insufficiency is directed at the fundamental etiologic mechanism A slow drip transfusion is necessitated in hemorrhage despite the contraindication in acute vessel closure In the presence of a paroxysmal cardiac irregularity the measures aimed at the acute cessation of the attack (p 851) are practiced with the greatest zeal manifestations of peripheral circulatory failure (shock) demand rapid restitution (p 937) with plasma infusion (p 3778) Patients with backward failure (p 941) in whom digitalization is indicated are entitled to the intravenous introduction of this potent remedy (p 858), for this purpose *digoxin* (p 859) is recommended using 1 or 2 cc of the

most frequent sites for difficulty are the heart the kidneys the retina and the central nervous system (hypertensive encephalopathy)

Cardiovascular Complications—The circulatory system bears the brunt of the mechanical strain of essential hypertension *Invariably there is en largement of the left ventricle* posteriorly and to the left (Fig 124) with increasing strain due to augmented peripheral resistance the ventricle hypertrophies and then dilates At this time the clinical manifestations *of backward failure* (p 941), *are superimposed At any time during the* course of these developments the patient may suffer attacks of *paroxysmal nocturnal dyspnea* (p 942) *pulmonary edema* (p 943) *angina pectoris* (p 890) *coronary insufficiency* (p 895) or *coronary occlusion* Often the cardiac complication is a herald symptom of the pre existent essential hypertension *whose presence may have been wholly unrecognized*

The onset of the complete cardiac breakdown is hastened in the pres ence of severe coronary arteriosclerosis, incidental infections persistent obesity or pulmonary emphysema With the appearance of congestive fail ure *the blood pressure frequently* but not *invariably falls* This occur rence is an evil rather than a good prognostic sign since it tends to aug ment the chances for the development of symptoms due to coronary insufficiency (p 895)

Valvular lesions may be found in hypertensive as well as in non hyper tensive *individuals When they are encountered they are not to be regarded* as true complications of the essential hypertensive state rather they rep resent rheumatic arteriosclerotic or luetic lesions which have chance asso ciation

Renal Complications—*Renal function is extraordinarily well maintained* in essential hypertension thus distinguishing the condition from the symp tomatic elevation of blood pressure that accompanies chronic glomerulo nephritis (p 2379) and the malignant phases of essential hypertension (p 908) *Urine studies often reveal polyuria but infrequent nocturia* small amounts of albumin are passed *intermittently* by many hyperten sives as well as by those who have normal blood pressure readings Occa sionally a small number of hyaline or granular casts are observed but leukocytes and erythrocytes should not be present except *on rare occa sions* The *presence of* a considerable *hematuria* or pyuria requires a thor ough study of the urinary tract for the possible presence of some organic lesion that may have predisposed to the hypertensive state

In the malignant phase of essential hypertension uremia occurs *in ap proximately 7 per cent of patients and may* prove to be an agonal com plication as later discussed

Neurologic Complications—In the early phases of an essential hyper tension, the complaints of *vertigo* (p 2020) and *headache* (p 914) are frequently encountered *As elsewhere stated* we are disinclined to attribute either of these symptoms to the hypertensive state and we make it a point of practice to inquire into other possible etiologic factors most particu larly the presence of an anxiety state

When the headache *is truly a* portion of the clinical syndrome of essen tial hypertension it has few consistent characteristics It may vary in its character severity and timing it seems to bear no constant relationship to the height of the blood pressure readings it may be *dull or throbbing*

ampouled solution diluted tenfold with saline This dose is the equivalent of 0 0005 to 0 001 gm (1/120 to 1/60 grain)

VASOVAGAL SYNCOPE

See *Forward Failure* (p 920)

CAROTID SINUS SYNCOPE

See *Forward Failure* (p 922)

CARDIAC NEUROSES (NEUROCIRCULATORY ASTHENIA DISORDERLY ACTION OF THE HEART SOLDIER S HEART EFFORT SYNDROME)

There are few clinical conditions which have given rise to more confusion and injustice than that which is most commonly labeled neurocirculatory asthenia Just as in other visceral neurogenic disorders such as the gastric neuroses (p 1767) the fundamental disturbance is an alteration in the reciprocal relationship of the subdivisions of the involuntary nervous system (*autonomic imbalance*) The syndrome may or may not be of psychogenic derivation (p 1395) There are no evidences of end organ disease and the condition should in no wise be regarded or labeled as a circulatory disorder

Etiology.—It is necessary to review the innervation of the heart (p 777) and blood vessels (p 782) in order to understand the clinical manifestations of neurocirculatory asthenia In general the vagal mechanism is cardio inhibitor while the adrenergic system is accelerator and augmentor The antagonism of these structures is controlled with nicety by a check mechanism which provides for smooth functioning in responses to effort Alterations in the adjustments give rise to the syndrome of neurocirculatory asthenia

An understanding of the reciprocal relationship is best illustrated by more obvious examples of errors in the mechanisms of timing A perfectly competent motor loses power and pickup if the spark is late a powerful golfer watches his ball slice or pull when the swing of the club head is out of rhythm with arms wrists or body The troubles of the duffer are unrelated to the quality of the golf course the clubs or the ball in the same sense the victim of neurocirculatory asthenia is not suffering from heart disease arterial degeneration or a psychosis he is certainly not a cardiac invalid

Pathogenesis—The mechanism responsible for neurocirculatory asthenia is an *autonomic imbalance* (p 1395) The reader is urged to familiarize himself with the subject matter on this disturbance before proceeding further with the reading of this section

While it is true that autonomic imbalance may be a mere instability of the involuntary nervous system there is no denial of the fact that it is frequently associated with preceded or followed by the various manifestations of the *neurosis* (p 1335) The condition may be exploited by a coward or a malingerer who is anxious to avoid or be discharged from military service but the implication is not necessarily absolute The experienced practitioner learns to withhold judgment relative to the char

its location varies but most commonly it is noted in the region of the occiput or the vertex Hypertensives often complain of headache on awakening with a tapering off as the day progresses others have attacks that seem to be truly migrainous (p 1512) indeed a disproportionately large number of those who eventually develop essential hypertension give clear cut histories of earlier *migraine* (p 1506)

ANGIOSPASM —*Of greater significance than the complaints of headache* vertigo irritability nervousness or insomnia are the more tangible complications that are believed to be *angiospastic* Often the patient notes transitory weakness or *paresthesia in an extremity or some other localized* area at times there is demonstrable motor weakness or anesthesia

CEREBRAL ACCIDENTS —More ominous are the incidents of true *cerebral hemorrhage or thrombosis* (p 1439) *which occur sooner or later in a fairly* large proportion of hypertensive individuals These cerebral accidents are

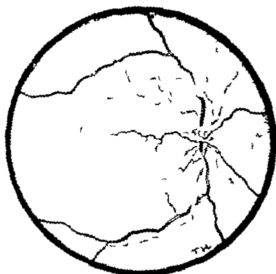


Fig 214 —Arteriosclerotic retino-pathy

unpredictable they bear no constant relationship to the height of the blood pressure they may occur in those with normal blood pressure and they may be significantly absent in those with protracted hyperpiesis

Hypertensive Encephalopathy —Hypertensive encephalopathy is an unusual complication of the syndrome of essential hypertension It is characterized by the sudden appearance of *convulsions* (p 1519) or *coma* (p 1794) Often a cerebral accident is preceded by a sudden marked elevation of tension there may be prodromal symptoms such as lethargy headache nausea vomiting localized paresthesias transitory blindness a fleeting hemiplegia or a monoplegia With or without these herald manifestations the classical episode consists of a severe tonic spasm with asphyxia due to diaphragmatic involvement after a few moments this phase gives way to a clonus which may be jacksonian or generalized The seizures gener

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acter of the individual suffering from neurocirculatory asthenia the victim may be an arrant coward and a shirker but he may also be the victim of grave injustice

Clinical Manifestations—The clinical manifestations of neurocirculatory asthenia are observed in civilian life but they become more obvious in times of war when men are called for military service The chief symptoms are *exertional* they consist of palpitation dyspnea precordial pain asthenia inability to execute heavy exercise and drilling premature exhaustion gasping respirations a tendency to sigh, feelings of faintness actual syncope insomnia headache dizziness, increased perspiration difficulty in swallowing tremor and episodes of flushing and pallor

Physical examination usually reveals the presence of many of the characteristics of the *neuroses* (p 1335) The individual is hypersensitive highly emotional and laden with anxieties and fears There are evidences of widespread *autonomic imbalance* as revealed by easy blushing and blanching *cold clammy hands profuse perspiration* excessive salivation or dryness of the mouth wide dilatation of the pupils and dermographia There may be tremors of the extended fingers and slight engorgement of the thyroid gland

Circulatory tests reveal nothing of significance the heart rate may be somewhat rapid and irregular due to a sinus tachycardia (p 874) or arrhythmia (p 877) the blood pressure may be labile the apex beat may be somewhat forcible but no other consistent changes can be recognized by the most extensive investigations including tests for vital capacity and electrocardiographic or roentgenologic studies The basal metabolic rate is normal in contradistinction to the finding in hyperthyroidism (p 1197) with which the condition is often confused

See **ECG 5**

Course and Prognosis—The patient with neurocirculatory asthenia rarely suffers from his fundamental complaint He does not progress to the stages of circulatory inefficiency or cardiac invalidism since his disorder prevents him from engaging in any strenuous occupation or exercise He is thoroughly useless as military material and constitutes a drain upon any army encampment At most he is eligible for non combat service in which capacity he is rarely efficient due mostly to the stigma that is attached to his affliction

In civilian life there is almost inevitably a transition to an *anxiety neurosis* (p 1347) with heart consciousness These individuals constitute a large bulk of the practice of most cardiologists to whom they eventually gravitate it is not easy for patient or practitioner to accept the degree and range of subjective symptoms without the suspicion that there must be present some disorder of the circulatory mechanism

Treatment—In times of combat, it is our opinion that army efficiency and the welfare of the individual are best served by placing all those who have neurocirculatory asthenia in non combat positions provided that the authorities can be assured that there is no element of malingering It is important to emphasize to these patients the opinion that they have no circulatory disorder they are not to be given circulatory drugs they are not referred to cardiac clinics or to those who specialize in cardiology they are not to be forbidden to smoke drink or engage in competitive

ally persist for only a few moments after which consciousness may be regained with surprising speed It is this rapidity of recovery that suggests that the hypertensive encephalopathy may be fundamentally angiospastic or the result of cerebral edema

The Eyes—Arteriosclerotic changes are usually observed in the retina in an essential hypertension Only occasionally are the fundus vessels normal more often the ophthalmoscope reveals narrowing and tortuosity of the arteries the presence of a brilliant light reflex some engorgement of the veins with obliteration of arterial crossings and fresh or old evidences of local hemorrhage

Epistaxis—Those who suffer from essential hypertension experience severe nosebleeds more frequently than non hypertensives The site of the epistaxis is usually the superficial capillaries of the mucosa of the lower turbinate or the septum The bleeding may be difficult to control

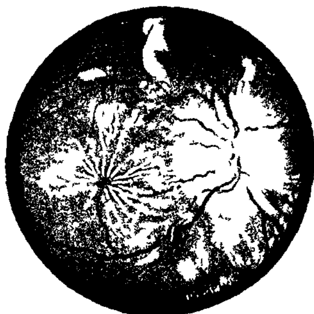


Fig 215—Fundus oculi in malignant hypertension

it may result in exsanguination and the development of manifestations of coronary insufficiency (p 895) The frequency of bleeding bears no direct relationship to the height of the arterial tension the precipitating factors are not understood

Malignant or Accelerated Phase of Essential Hypertension—*Those* patients with essential hypertension who do not succumb to cardiac or cerebral complications often progress to the malignant phase with severe renal damage and a fatal *uremia* (p 2276) These complications are experienced in perhaps 5 to 10 per cent of all the afflicted they are regarded as sudden accelerations of the disturbance with the production of necrosis of the vessel walls and hemorrhage

The malignant phase of essential hypertension occurs more frequently in the younger *hypertensive individuals* It may be encountered in those

Courtesy of The Ophthalmoscope under copyright of The American Optical Co

exercise they are not to be plied with endocrine products adrenergic or cholinergic drugs they should not be subjected to surgical procedures such as thyroidectomy unilateral adrenalectomy or interference with the fibers of the involuntary nervous system

The positive program for the neurocirculatory asthenic is one of complete *reassurance* as to organ integrity Corrective exercise (p 37-7) is advised Psychotherapy is attempted at first by non technical methods and later if necessary by an accredited psychiatrist (p 1328)

with a known preexistent elevation of blood pressure or it may develop as an apparently primary disorder In either instance there is the sudden onset of severe headache the blood pressure rises sharply more marked in the diastolic than the systolic reading the ophthalmoscopic picture reveals a papilledema (p 1577) with several diopters of elevation and vascular changes exudates and hemorrhages may be noted (p 1578) At this time there are evidences of marked renal insufficiency blood chemical *studies reveal the presence of azotemia and there is the rapid development* of the clinical syndrome of uremia (p 2270)

Often the manifestations of a disturbance in the realm of the central nervous system dominate the picture suggesting the possibility of the presence of a brain tumor (p 1419) The headache is severe and intractable there may be stiffness of the neck nausea vomiting convulsions and an elevation of spinal fluid pressure These with the fundus picture strongly suggest that there is some disturbance in intracranial pressure relationship but the height of the diastolic pressure serves to direct the practitioner to the more likely presence of the hypertensive disorder

Prognosis—The determination of life expectancy in an individual who has essential hypertension is fraught with hazard because of the many unpredictable variables Uncomplicated essential hypertension may be *well tolerated for many years without incident the patient finally suc*cumbing to some totally unrelated condition Conversely there is no way of determining when a complication may be superimposed when the phase of malignant hypertension may be encountered or when a hypertensive encephalopathy may supervene

Favorable Prognosis—Every effort should be made to give a favorable prognosis in an essential hypertension So devastating is the effect of a superimposed anxiety state that the practitioner often hesitates to acquaint his patient with the fact that his blood pressure reading is elevated Often he seeks to temper the blow by the casual statement that the blood pressure is up a bit' and if the direct question is asked concerning the exact figures a little judicious lying is often a justifiable portion of the therapeutic program (Fig 1178 p 3040)

The practitioner who attempts to protect his hypertensive patient by minimizing the condition or falsifying the height of the reading has the additional responsibility of protecting his professional reputation He should acquaint the most responsible member of the family with the more exact details and the possible consequences By this same act the welfare of the patient is often bettered since follow up visits are then encouraged by the lay friend or advisor under these circumstances the insistence upon continued observation does not carry the same threat as it would if initiated by the professional advisor

The main value of a favorable prognosis relates to prophylactic therapy This maneuver may effectually prevent the patient from developing an *anxiety neurosis* (p 1347) with blood pressure ophobia and cardiac consciousness It has been our belief and experience that most of the subjective symptoms associated with essential hypertension are psychogenically induced and relieved by assurance and the prescription of simple sedation

The Guarded or Unfavorable Prognosis—Because of the necessity of

CHAPTER 40

PHYSIOLOGICAL DISTURBANCES OF THE CIRCULATORY SYSTEM ALTERATIONS IN VASCULAR TENSION

ESSENTIAL HYPERTENSION

ESSENTIAL hypertension is a clinical syndrome in which the patient has an abnormal elevation of blood pressure without demonstrable causative lesions of an organic nature The condition *should not* be diagnosed *until* the etiologic factors of symptomatic hypertension (p 910) have been sought and found to be conspicuous by their absence

Etiology and Pathogenesis —A variety of factors contribute to the etiology and pathogenesis of essential hypertension These include hereditary environmental neurogenic endocrinologic metabolic mechanical and humoral influences

Hereditary Factors —There seems to be a definite familial factor in hypertension Whether this is truly hereditary or whether it results from common environmental conditions of stress and strain cannot be presently determined

Psychogenic Influences —There is much to suggest that essential hypertension is one of the prices paid for civilization To the best of present knowledge the affliction is not seen in the lower animals and does *not* occur among aborigines The stress and strain of modern existence may initiate the factors productive of the disturbance Through the mediation of the involuntary nervous system and its influences over the glands of internal secretion there may be effected the changes in the arterial bed and the kidneys later to be described

Autonomic Imbalance —Hypertension is readily produced by stimulation of the adrenergic subdivision of the involuntary nervous system Were we in possession of knowledge relative to the factors that control the tonicity of this important neurogenic pathway (p 1390) it might be possible to elucidate the nature and character of essential hypertension Many fascinating theories present themselves for speculative flights of fancy There is the possibility that the stress and strain of civilization so alters the tonicity of the involuntary nervous system as to favor adrenergia with resultant vasoconstriction and elevation of vascular tension There is the possibility that there exists a hypothalamic center in which this same mechanism is operative at a higher level There is the possibility that the neurogenic mechanism initiates some disturbance in the endocrinological economy whereby such substances as adrenal cortical ex

ally persist for only a few moments after which consciousness may be regained with surprising speed It is this rapidity of recovery that suggests that the hypertensive encephalopathy may be fundamentally angiospastic or the result of cerebral edema

The Eyes—Arteriosclerotic changes are usually observed in the retina in an essential hypertension Only occasionally are the fundus vessels normal more often the ophthalmoscope reveals narrowing and tortuosity of the arteries the presence of a brilliant light reflex, some engorgement of the veins with obliteration of arterial crossings and fresh or old evidences of local hemorrhage

Epistaxis—Those who suffer from essential hypertension experience severe nosebleeds more frequently than non hypertensives The site of the epistaxis is usually the superficial capillaries of the mucosa of the lower turbinate or the septum The bleeding may be difficult to control

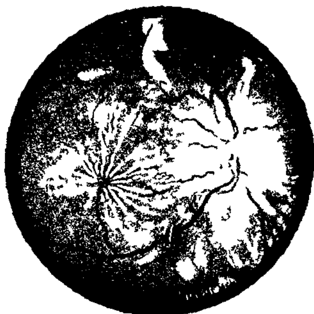


Fig 21 —Fundus oculi in malignant hypertension

it may result in exsanguination and the development of manifestations of coronary insufficiency (p 895) The frequency of bleeding bears no direct relationship to the height of the arterial tension the precipitating factors are not understood

Malignant or Accelerated Phase of Essential Hypertension—Those patients with essential hypertension who do not succumb to cardiac or cerebral complications often progress to the malignant phase with severe renal damage and a fatal *uremia* (p 2276) These complications are experienced in perhaps 5 to 10 per cent of all the afflicted they are regarded as sudden accelerations of the disturbance with the production of necrosis of the vessel walls and hemorrhage

The malignant phase of essential hypertension occurs more frequently in the younger hypertensive individuals It may be encountered in those

* Courtesy of The Ophthalmoscope under copyright of The American Optical Co

tract (p 1267) or adrenalin (p 3877) are hypersecreted with the production of hyperpiesis as the direct result of their quantitative presence or through their effects on sensitized nerve endings

However fanciful may be these hypotheses practical surgeons have shown that interruption of the adrenergic pathways has some utility in the management of hypertensive disease (p 914)

Endocrinopathies —The presence of hypertension in certain of the profound endocrinopathies has led to reasonable speculation as to the importance of ductless glandular secretions in the pathogenesis of essential hypertension Elevations of blood pressure are observed with adrenal cortical tumors (p 1278) with basophile adenomas of the anterior pituitary gland (p 1175) and with pheochromocytomas (p 1264) It is reasonable to pose the question as to whether the accompanying hypertension is a mere pathologic manifestation or whether it represents a quantitative change in a physiological process These speculations are of more than academic importance since they have led surgeons to attempt the treatment of essential hypertension by denervation of the adrenal glands and by unilateral adrenalectomy with denervation of the remaining side They have caused roentgenologists to suggest the therapeutic approach to the problem by irradiation of the sella turcica with all of the attendant implications

Obesity —The patient with essential hypertension is usually obese though this is not necessarily true The relationship of obesity to the hypertension presents at least two problems Are both conditions the result of a single fundamental etiologic factor such as an endocrinopathy? Is the hypertension partially the result of obesity and in the nature of a work hypertrophy?

Whatever may be decided as the final role of obesity in hypertension certainly the practitioner knows that weight reduction is essential for the successful accomplishment of any therapeutic program (p 696)

Increased Resistance of the Arterial Bed —The Goldblatt experiments elsewhere described (p 2273) leave little doubt that it is possible to produce hypertension by progressive constriction of the renal artery of the dog The Goldblatt animals show no evidence at first of renal excretory insufficiency later they may go on to develop the manifestations of malignant hypertension (p 908) with papilledema uremia and arteriolar necrosis

Without detracting from the importance of the Goldblatt experiment many problems remain to be decided relative to the pathogenesis of human essential hypertension The most important of these are (*1*) The clarification of the fundamental cause that produces narrowing of the arteriolar bed and (*2*) the elucidation of the link between vascular constriction and hyperpiesis

Humoral Influences —The ischemic kidney liberates a substance called *renin* In those in whom hypertension is produced renin is modified by a pseudoglobulin fraction of the plasma for the production of *angiotonin* which may cause elevation of arterial pressure In the normal non hypertensive individual serum contains an *antirenin* which may neutralize the effects of the hypertensive substance

Attention is directed to the therapeutic implications of the humoral agencies these are unaffected by denervation procedures (p 914) their

to the patient s expense We oppose the use of *aconite* and have seen nothing of value following the administration of preparations derived from *mistletoe watermelon seeds* or *onions* We have no confidence in *insulin free pancreatic extracts* or other *tissue derivatives* advertised as having hypotensive effects We do not prescribe *iodides* which promise no benefit in non syphilitics and whose prolonged use is inevitably accompanied by manifestations of iodism (p 612)

Because of their carcinogenic potentialities we are fearful of the protracted use of *estrogens* in the hypertensive phenomena that are frequently encountered at the time of the *menopause* We have not observed any specific hypotensive accomplishment following the continued use of *an drogen* in climacteric males The use of endocrine products over any long period of time involves an expense which is far from negligible in the management of any protracted disorder

While those who are exponents of the humoral theory of the pathogen esis of hypertension (p 901) hold high promise for the isolation of a blood pres ure reducing principle the present products seem without merit and are difficult to obtain

The Way of Life —In few medical conditions is it more important than in essential hypertension to make inquiries into the way of life (p 3473) The practitioner reviews with his patient his every activity from rising until retiring he attempts to preserve for his patient those essential activities without whose performance life would be meaningless he advises avoidance of those duties obligations and chores which con tribute nothing to the art of living and add considerably to fatigue and nervous tension

The Rest Cure —Those patients who have opportunity for self indul gence often profit by a *rest cure* taken under institutional conditions (p 3755) Others who must carry out their activities are often benefited by a *cure day* (p 3755) taken once each week or by an occasional week end spent lolling in bed

The more vigorous particularly those who have a burdensome household may often be sent off on a holiday without family encumbrances Wealthy patients are justified in spending their resources on spa therapy (p 3764) which provides a trip away from the domestic scene and a mechanism for escape (p 3761)

Exercise—It is a grave blunder to forbid exercise under these circum stances the patient becomes flabby and fat his anxiety is increased and his simple pleasures are significantly reduced The practitioner must be certain that his patient keeps in reasonably good physical condition The best exercise is walking for a minimum of two miles at least once daily indulgence in sailing boating fishing gardening or non competitive golf is encouraged

Proscriptions—In the management of each individual with essential hypertension it becomes necessary to discuss policies concerning the uses of caffeine tobacco and alcohol Our own attitude in asymptomatic hy pertension is one of complete inconsistency since we are guided almost exclusively by the patient s reaction to the presenting problem *We are among those who find no fault with the moderate use of caffeine and alco hol* In the instance of the former by moderation we mean two or three

isolation may provide a pharmacodynamic approach to a presently insoluble problem

Summary—Despite intensive investigation of essential hypertension the etiology and pathogenesis of this condition remain obscure From the standpoint of clinical practice however it may not be amiss to attempt a hypothesis by which an intelligent therapeutic program may be promulgated With this apology it is suggested that the series of events leading to hypertension may be somewhat in the nature of the following

1 As the result of stress and strain of civilization an *autonomic imbalance* is established whereby the balance of power is tilted in favor of the adrenergic system



Fig 212—Late changes in the glomerulus in an arteriosclerotic kidney Collapse of tuft with great thickening of Bowman s capsule Atrophy of adjacent tubules *

2 *Adrenergia* produces vasoconstriction with narrowing of the arteriolar bed most particularly in the kidneys
3 *Renal ischemia* is followed by or associated with the production of renin and angiotonin or the inactivation of antirenin
4 Diminution in or absence of the renin neutralizing substance results in the transformation of renin to angiotonin with augmentation of the previously established adrenergic hyperpiesis It may be that the transition from *adrenergic hypertension* to *angiotonin hypertension* determines the clinical mutation from the relatively benign essential hypertension to the malignant form with *hypertensive encephalopathy* (p 907)

* MacCallum Textbook of Pathology

titioner follows the principle of 'skilful neglect' when symptomatic disturbances present themselves the long range view requires active consideration of elective surgical intervention at a time when the operative procedure holds some promise for a successful issue

Asymptomatic Essential Hypertension —The management of asymptomatic hypertension involves psychotherapy sedation weight reduction 'specific' drug therapy and the avoidance of provocative etiologic agencies

Psychotherapy—The life liberty and pursuit of happiness of the hypertensive patient may be dependent mainly upon his practitioner's psychotherapeutic approach to the problem The alarmist who regales his unfortunate victim with accurate scientific data concerning his outlook will surely superimpose the symptoms of an *anxiety neurosis* (p 1347) and thus create a vicious cycle By contrast the more thoughtful and considerate practitioner friend metes out liberal doses of *assurance* and *reassurance* often at the jeopardy of his professional reputation He states merely that the blood pressure has a tendency to be elevated he avoids giving exact readings he tries to prevent 'sphygmomanometer consciousness' and takes blood pressure readings more or less under duress Often he states that his own blood pressure has a tendency to fluctuate and he makes every effort to leave his patient with the conviction that the affliction is relatively unimportant but of sufficient significance so that the simple directions merit obedient consideration

Weight Reduction—There must be no compromise as to the importance of following a *low calory diet* (p 669) It is not unusual to find a loss of 10 to 15 pounds in an obese individual, accompanied by a drop of 40 to 50 mm of mercury in systolic readings Those patients who have a diminution in the basal metabolic rate (p 716) are required to take *thyroid extract* (p 1189) in corrective and then maintenance dosage To counteract lay misinformation the patient is fortified with the knowledge that thyroid extract does not elevate blood pressure

Sedation and Hypnosis—The hypersensitivity and tenseness of most patients with essential hypertension justify the uses of sedatives following each meal and a hypnotic at bedtime For the former we prefer doses of sodium phenobarbital 16 mg (¼ grain) three times daily after meals for a sleeping potion we prefer sodium seconal, 0 1 gm (1½ grains) at bedtime

A favorite prescription of many of the older practitioners is under noted

℞	Sodium Bromide	15.0
	Chloral Hydrate	5.0
	Syrup of Orange q.s ad	60 0
	Sig Teaspoonful every 4 hrs	

Specific Drug Therapy—We have no faith in any of the allegedly hypotensive drugs The *nitrates* and *nitrites* (p 3892) have a transitory effect in lowering blood pressure in the instance of *erythrol tetranitrate* (p 3893) which has a more prolonged effect the accompanying headache is often sufficiently severe to demand abandonment of the therapeutic measure We regard the use of the *sulfocyanates* as excessively *toxic in* proportion to their accomplishments The xanthines particularly *aminophylline* accomplish little in our experience and they add considerably

Pathology —The pathologic lesions associated with essential hypertension are more likely the effect of the disturbance than its cause The most marked changes are found in the vessels the kidneys and the cerebrum

Renal Lesion —In essential hypertension the kidney may appear granular and only slightly contracted the organ is firm it cuts with difficulty revealing both fine and coarse lobulations The capsule is adherent indicating the presence of fibrosis Microscopically many of the glomeruli are seen to be hyalinized and the arteriolar lesions next to be described appear in an advanced form

Arteriolar Lesion —The patient with essential hypertension may reveal excessive degenerative changes in the arterioles Both intima and media are involved with resultant narrowing of the lumen The arteriolar change



Fig 213 —Hyaline changes in arteriole and glomerulus Arteriosclerotic nephritis

is usually most marked in the kidney but is also seen in the other organs such as spleen pancreas liver and brain

Heart —In an essential hypertension of any duration there is usually an associated hypertrophy and dilatation of the heart The arteriolar lesion may be visible in the coronary arteries but such arteriosclerosis as is present in the aorta seems purely incidental and unrelated to the fundamental physiological disturbance

Other Changes —On rare occasions a natural Goldblatt kidney is observed as the result of some surgical disease of the kidney The renal ischemia may be the result of congenital atrophy (p 2291) a pyelonephritic contracted kidney or one that is the seat of polycystic disease These

ence of any of the unfavorable prognostic implications (p 909) However the procedure should not be considered in those beyond the age of forty and in those with demonstrable renal damage cardiovascular complications or advanced retinal changes

In selecting their material most surgeons employ the cold pressor and sedation tests They hesitate attempting the operative procedure in the patient who does not show marked fluctuation since there is little hope of benefit if blood pressure readings are at a fixed level

As in all other operations of election there is wide diversity concerning indications Enthusiasts favor surgical intervention in any individual with significant essential hypertension of any duration they regard the procedure as prophylactic in asymptomatic essential hypertension Opponents of the method point to its limitations with particular reference to the fact that surgery does not alter the fundamental causative mechanism and has no effect to the best of present knowledge upon the humoral components of the syndrome (p 901)

Our attitude leans toward *conservatism* we believe that the indications for operation are very rarely encountered in private practice and we prefer to temporize in asymptomatic conditions and await the earliest manifestations of the unfavorable prognostic implications (p 910) By this attitude the majority of those with essential hypertension need never consider operative procedure those who are advised to consult the surgeon have not yet reached the point where their manifestations are wholly irreversible

Preoperative Preparation Operative Morbidity and Mortality and Operative Results—Preceding operation the patient is treated intensively according to the principles outlined in the management of asymptomatic hypertension (p 912) The orders call for bed rest weight reduction and the use of sedatives and hypnotics

The immediate *operative risk* in the most expert hands approximates 2 per cent The more serious *postoperative complications* include impotence in the male (p 1304) and postural hypotension which may persist for several weeks to as long as a year

The *operative results* are not as striking as the enthusiasts would wish. The fall in blood pressure is often temporary and may be followed by a return to preoperative levels Headache vertigo and palpitation are often ameliorated out of all proportion to the blood pressure effects In certain spectacular instances fundus changes including papilledema (p 908) have receded but these happy eventualities are certainly in the minority

Nonoperative Treatment of Progressive Essential Hypertension with or without Complications—Those patients with essential hypertension who develop symptoms and complications but who are not eligible for surgical interference present many difficulties in management In general the practitioner follows along the general principles laid down for the treatment of asymptomatic hypertension (p 912)

Two innovations in dietotherapy merit consideration Reduction in sodium intake made possible by dialysis of milk appears to reduce hypertension in the experimental animal and in human subjects Similarly a rice-fruit sugar intake of 2000 calories (containing 20 gm of protein 5 gm of fat 400 gm of carbohydrate 0 2 gm of sodium and 0 15 gm of chloride) with

gross renal changes however are the exception rather than the rule, they do indicate the necessity of obtaining all the visual information that can be obtained regarding the kidney in the hope that a remediable condition may be discovered in the individual patient

Beyond the changes in the kidneys there may also be late manifestations such as coronary thrombosis areas of myocardial infarction cerebral arteriosclerosis with hemorrhage thrombosis and softening

Clinical Manifestations—Essential hypertension remains asymptomatic for long periods of time In the majority of instances the diagnosis is established when blood pressure readings are taken in the course of the routine physical examination or the investigation of some other unrelated complaint

Blood Pressure Readings—The determination of the blood pressure level is as simple as it may be confusing As has been elsewhere emphasized (p 3480) there is tremendous variation and marked lability in readings Basal determinations are not taken with the care exercised in calculating the metabolic rate with the result that many high strung and sensitive individuals are labeled hypertensive for no other reason than that a single reading may during a period of anxiety and excitement prove to be somewhat higher than the accepted norms which are published in life insurance statistics

THE NORMAL—It is as futile to attempt a statement of normal blood pressure as it would be to attempt to define normal weight normal height or normal intelligence In fact the difficulty is made even greater by the fact that whereas height and weight measurements for the same individual are relatively constant blood pressure readings may be so labile that variations up to 100 per cent may be observed over the course of a few days hours or even minutes

FLUCTUATIONS—Those who see the patient but once in the course of casual examination as in the instance of life insurance examiners or those who determine the physical status for military qualifications are in a much more difficult position than the practitioner with whom the patient is on easier terms of contact It is a not unusual experience for the practitioner to be confronted with a situation wherein a patient with normal blood pressure reports that he has been rejected for life insurance an army commission or some other desired post merely because the casual examiner has reported a high reading of the mercury column Many of the benefits of preventive medicine and health examinations are negated by the anxiety state created by the failure of routine examiners to appreciate the inconstancy of blood pressure readings

Despite the emphasis upon fluctuations of blood pressure the practitioner must have some standards by which he can determine normality and its deviations In general it may be stated that the zone of suspicion rests between 130 and 160 systolic and 80 to 90 diastolic pressures the zone of absolute hypertension is that in which there are repeated readings in excess of 160/90 The readings are the more significant if they are taken under relatively basal conditions

GRADIENT OF ARTERIAL PRESSURE—Of greater importance to the practitioner who has the opportunity of seeing his patient over a long span of time is a rise in the arterial pressure gradient a reading of 130 is of

cups of coffee or tea daily In the instance of alcohol moderation is defined as a single drink at the termination of the daily activity and another some time after the evening meal and before retiring the first drink may be whiskey, a cocktail or a glass of wine the second drink may be a glass of wine a bottle of beer or a highball Those patients who greatly enjoy the effects of the cup or the glass that cheers are encouraged to continue with their small vice those who are fearful of possible harm and eager to carry out a highly restricted program are advised to use caffeine substitutes and soft drinks

Our attitude toward *tobacco* is much less lenient We urge the patient with asymptomatic hypertension to stop smoking entirely We are not completely impressed by the scientific evidence of the relationship between smoking and hypertension but we believe that the pleasures derived from the habit are too little to justify the potential hazards With characteristic inconsistency we acquiesce to the continuation of smoking in inveterate users of tobacco and those whose tenseness and nervousness would be too greatly augmented by their attempts at *self negation* If smoking is continued we do urge *rejection of cigars and pipes cigarettes* are smoked in a holder preferably with a filter and the 'limit is ten daily

Dietotherapy—We do not favor restrictions on protein water or salt in the management of essential hypertension Blood pressure is not lowered by these dietary bans it is not elevated when these substances are given in excess

The Treatment of Headache—We have elsewhere commented (p 1510) on the relative infrequency with which the headache which accompanies essential hypertension is derived from the cardiovascular disorder Most often it arises as the result of some other operating mechanism whose *cause must be determined and treated in the manner elsewhere described*

See *The General Management of Headache* (p 1510)

If it is firmly established that the headache is part of the hypertensive disease considerable relief is often afforded by the use of *sedatives* and *hypnotics* (p 3837) Should these measures prove unsuccessful each dose may be fortified by the administration of a *headache capsule* (p 1508) or a tablet containing *acetylsalicylic acid* (p 3833) or one of its related substances (p 3832) Histamine desensitization may be tried using 0 05 mg (1/200 gr) daily and injecting increasing doses at daily intervals

The Treatment of Symptomatic Essential Hypertension with or without Complications—Once essential hypertension has progressed to the symptomatic stage or that of the development of complications the practitioner is required to discuss with frankness the prognosis of the affliction (p 909) and the advisability of surgical intervention

Surgical Technics—A variety of surgical procedures have been attempted in efforts to control essential hypertension The most effective of the present operative approaches involves removal of virtually the entire great splanchnic nerve with division of all its aortic branches coupled with interruption of the communicating rami of D9 D10 D11 D12 and L1 and excision of the sympathetic trunk *in this area* The operation is carried out first on one side and then 10 days later on the other side (Smithwick)

Indications—Operative interference merits consideration in the pres

genuine significance when it is known that the previous level approximated 100 or 110 by contrast the reading of 130 is of no significance in an individual whose usual range extended from 120 to 170

See *Differential Diagnosis of Systolic Hypertension* (p 910)

DIASTOLIC PRESSURES —Contrary to the general impression diastolic pressures are also labile The fluctuations are not as great as the systolic but they are proportionately as inconstant Thus the patient who has a reading of 120/80 at any given time and who under emotional stress has a systolic rise to 180 (+50 per cent) will probably manifest a diastolic reading of 120 (+50 per cent) at the same time

See *Differential Diagnosis of Diastolic Hypertension* (p 918)

PULSE PRESSURE —The presence of a large pulse pressure in an individual with essential hypertension suggests the existence of sclerosis and dilatation of the aorta A reading of 200/95 for example in an elderly individual suggests that the aorta has lost most of its elasticity due to degenerative change

See *Differential Diagnosis of Pulse Pressures* (p 918)

General Habitus —In general the hypertensive is a sthenic heavy set obese red faced individual Exceptions to the rule are frequent essential hypertension may be encountered in pale thin ptotic patients who seem most unlikely candidates

Subjective Symptoms —The subjective symptoms of essential hypertension are often in the nature of an *anxiety neurosis* (p 1347) that is created unwittingly when the patient is told that he suffers from high blood pressure It is our practice to assume that the complaints of the patient with essential hypertension are due to some other cause unless everything else can be excluded Verification of this attitude is confirmed by the frequency with which high levels of blood pressure are associated with well being so long as the patient is ignorant of the reading and the relief of symptoms despite failure to reduce the pressure when the patient is given reassurance and a simple sedative

The common complaints that accompany essential hypertension include nervousness vertigo irritability weakness insomnia precordial oppression shortness of breath and headache The last of these always attributed to the hyperpiesia when an elevated reading is encountered is in our experience almost invariably the result of some other condition

See *Differential Diagnosis of Headache* (p 1512)

Autonomic Imbalance —The majority of those who suffer from essential hypertension present evidences of instability of the involuntary nervous system (p 1395) as elsewhere described It is not at all uncommon to note vasomotor instability as manifested by cold and clammy hands and feet excessive sweating a tachycardia tremor of the extended fingers flushing and blanching of the skin dermographia and some slight swelling of the thyroid gland It is for this reason that essential hypertension is often confused with hyperthyroidism requiring an estimation of the *basal metabolic rate* and an observation of the therapeutic response to *iodide* before definitive diagnosis can be made

Complications —The onset of complications is almost inevitable in any individual who suffers from essential hypertension So common are these occurrences that they may be considered components of the disease The

comes a clinical problem only when it is of increasing degree or when the practitioner suspects that it is related to such symptoms as asthenia and easy fatigability

Treatment—Asymptomatic hypotension requires no therapy The practitioner owes it to himself however to acquaint the patient with the reading lest at some future examination this be regarded as a significant deviation from the norm

DIFFERENTIAL DIAGNOSIS OF

Hypotension

Hypotension is often masked by the emotional rise that occurs when patients first visit the doctor s office It is of importance only when it is sustained, when the readings progressively diminish and when there is discrepancy of more than 15 or 20 mm between recumbent and upright readings (orthostatic hypotension)

CAUSE	DIAGNOSTIC FEATURES
Physiologic	Particularly in patients of asthenic habitus (p 3488)
Orthostatic	Differences in excess of 15 to 20 mm between supine and erect readings May be associated with faintne s dizzine s and attacks of syncope
Fatigue and Debility	After prolonged physical and mental strain. In convalescence from debilitating illness or surgical procedure
Anemia	Particularly with acute hemorrhage Get hemogram and hematocrit (p 1057)
Forward Failure	In syncope and shock With increased hematocrit values (p 928)
Cardiac Tamponade	With compression due to pericardial effusion or incasement (p 872) Note effect of aspiration Consider surgical consultation in adhesive pericarditis
Coronary Insufficiency and Occlusion	Falling gradient of blood pressure a opposed to rise in angina pectoris (p 895 98_)
Carotid Sinus Syndrome	From pressure on sensitive trigger mechanism in neck. May be a sociated with attacks of syncope
Adrenal Cortical Insufficiency	In Addison s disease with pigmentation and profound asthenia Therapeutic response to sodium and specific hormone (p 925)
Dissecting Aneurysm	Acute hypotension associated with excruciating pain and evidences of progressively increasing vascular tumor (p 99)
Backward Failure	In terminal stages particularly with myomalacia (p 941)

In those patients whose hypotension is symptomatic particularly when associated with fatigue the way of life merits consideration A complete physical examination should be performed for the purpose of disclosing unsuspected insidious disease

The wary practitioner recalls instances of occult malignancy tuberculosis blood dyscrasias and internal bleedings in which the herald manifes

The bathroom should also contain a large pan with a cover Into this pan are emptied urine enema returns and stool together with an equal volume of the cresol solution At the expiration of one and preferably two hours the contents of this pan are flushed down the hopper

Disposable tissues and dressings are burned or incinerated The nurse s gloves are sterilized by the use of soap and water followed by immersion in the bichloride solution The nurse s gowns and rubber apron are hung in the bathroom A gown is also provided for the physician If possible he keeps an additional stethoscope Failing this the stethoscope is cleansed with the bichloride solution followed by alcohol

In respiratory diseases masks are kept available These can be im provised with gauze employing at least eight layers

The Room —Whenever possible the practitioner should insist that the infected patient occupy a room alone It is permissible to bring a cot or another single bed into the room for the nurse or attendant The members of the family must sleep elsewhere The room should be near a bathroom All other considerations are secondary If there is a choice a pleasant sunny room that is easily ventilated and readily heated is preferred The room should be stripped of all except the essential furniture Hangings are taken down The rug is removed A simple cot or preferably a hospital bed replaces the more elaborate article of furniture

There is increasing recognition of the importance of environmental con tamination in the propagation of disease Hemolytic streptococci have been isolated from desiccated secretions redistributed into the atmosphere in particulate form during bedmaking and dry sweeping The organism may survive for many months in blankets which probably constitute a more important source of aerial contamination than do droplets expelled directly by the infected person Dispersal of infectious material may be terminated by oiling of floors treating the bed clothes with an oily emulsion and reducing the infectivity of contaminated atmosphere by generous use of vapor of triethylene glycol The oil emulsion that has been recommended as a final rinse in the laundering of bed clothes consists of

Mineral oil	88 0
Oleic acid	8 9
Triethanolamine	3 9
Lecith n	0 1

The base is poured into water and mixed well to form a milky emulsion of 1 or 2 per cent strength

The Bed —A hospital type of bed should be purchased or borrowed if possible The ordinary cot i so low that nursing procedures are executed with difficulty The hospital bed because of its height adds to nursing comfort Additionally the hospital bed is provided with equipment to raise the head This permits the patient to sit upright or semirecumbent during feeding A device that bends at the knees prevents the upright patient from slipping

The Mattress —No matter what type of bed is used it is imperative that a stiff mattress be employed Soft mattresses with central sloughs appear comfortable but produce backstrain as well as points of pressure productive of decubitus ulcers If a good firm mattress cannot be pur

NONSPECIFIC TREATMENT OF THE INFECTED PATIENT

While he is occupied with diagnostic measures and attempts at public health control the general practitioner is required to devote his close attention to the individual who is afflicted with the infectious manifestations In the material that follows the general principles of treatment common to all infectious states are detailed so that it is not necessary in each single discussion to repeat these recommendations

INSTITUTIONALIZATION

While there are many theoretical reasons for institutionalizing the private patient with an infectious disease practical considerations are such that the vast majority of patients with communicable disease are treated in the home Even in the larger cities there are not available accommodations for patients with infectious diseases Many patients and particularly the parents of an infected child object to transfer to a public ward The practitioner who sends his patient to the infectious disease hospital immediately loses control of the clinical condition

NURSING CARE THE SICK ROOM

Wherever feasible the practitioner should insist on the use of registered nurses throughout the day and night If nursing care is out of the question a member of the family is instructed in the technic of the management of the infectious patient

Immunization of Nurse —If the nurse and members of the household have not had the infection antigen immunization (p 78) or chemoprophylaxis is indicated Sulfadiazine in daily doses of 2 gm (30 grains) is particularly advocated in streptococcal gonococcal and meningococcal invasions

Protection of Nurse —The nursing attendant should wear a rubber apron while handling the patient In the treatment of the respiratory diseases she should be masked Rubber gloves are to be worn for any procedure that requires contact with the body or secretions of the patient

Antiseptics and Disinfectants —The nurse should have several solutions available for antisepsis and disinfection

The hand basin is supplied with soap and a stiff brush The hands of all attendants including the physician must be scrubbed thoroughly before and after handling the patient The hands are dried with disposable tissue later to be burned

Next to the hand basin there should be a bowl containing bichloride of mercury 1 1000 stained with methylene blue After the hands have been thoroughly washed and rinsed in cold water they are immersed for at least three minutes in the bichloride solution They are then patted dry with the disposable tissue and treated with a glycerine in rose water hand lotion to prevent excessive drying and redness of the skin

The nurse must keep the bathtub filled with 2 per cent liquor cresolis compositus Linens including bedclothes bed linens handkerchiefs and napkins are washed first in soap and water to remove gross stains and then thrown into the cresol solution in the bathtub They should soak for at least two hours and preferably overnight after which they are wrung dry and sent to the laundry or washed on the premises

supplementary vitamins calcium and iron, is reported to alleviate headache and edema, decrease heart size, diminish blood pressure and clear retinopathy in hospitalized patients The basis of the food intake is boiled or steamed rice (300 gm) served with fruit juices and sugar but avoiding salt milk and fat The routine merits trial Considerable observation will be required to evaluate the specific effects of the diet aside from the factors of weight reduction hospitalization and psychotherapy

Complications such as *angina pectoris* (p 890), *coronary insufficiency* (p 895) *backward failure* (p 941), *uremia* (p 2278), *cerebral thrombosis* (p 1444) or *cardiac arrhythmias* (p 873) are symptomatically treated as in non hypertensive states

The Treatment of Hypertensive Encephalopathy—The presence of hypertensive encephalopathy requires the prompt institution of intensive therapeutic endeavors These aim essentially at the control of the *cerebral edema* which is possibly responsible for the presenting symptomatology

Intravenous Sugars—The intravenous injection of hypertonic solutions of the sugars is often effective in reducing cerebral edema and relieving the immediate symptoms As much as 200 cc of 50 per cent *dextrose* or *sucrose* may be employed by slow injection sucrose is preferred to dextrose since its use is not followed by a secondary rise in intracranial pressure The injections may be repeated several times during each twenty four hour period if necessary

Phlebotomy—It is often advisable to precede the intravenous injection of the hypertonic sugar by a generous phlebotomy Following the withdrawal of the blood, the sugar solution is introduced by slow intravenous drip so that both procedures are accomplished with a single venipuncture

Lumbar Puncture—Should the result of the combined efforts of phlebotomy and sugar injection prove unsatisfactory, a spinal tap is worthy of consideration Fluid is removed very slowly lest there be precipitated a herniation of the brain stem into the foramen magnum If the spinal tap proves to be beneficial it may be repeated at intervals of twelve to twenty four hours or as long as improvement continues to be observed

Magnesium Sulfate—Under institutional conditions intravenous injections of 20 cc of 10 per cent magnesium sulfate may be hazarded if the less dangerous methods prove to be futile and if the patient is suffering from convulsions (p 1519) Because of the potential respiratory depressant action of the magnesium ion *calcium gluconate* is kept readily available in a 20 cc syringe so that it can be injected intravenously without delay if the need arises

Soluble Barbiturates—The control of convulsive phenomena also may be attempted through the intravenous use of the soluble barbiturates (*sodium pentothal* or *sodium luminal*) If these preparations are not available, the slow intravenous injection of 2 to 4 cc of *paraldehyde* (p 3844) is worthy of trial

HYPOTENSION

Low blood pressure of itself is not a disease lay opinion to the contrary notwithstanding Many asthenic individuals and others of normal habitus may have readings as low as 90 systolic and 55 diastolic without evidence of ill health or incursion upon energy resources Hypotension be

Blackout in Airplane Pilots —The visual disturbances usually occur 1 or 2 seconds after the force is applied and quickly disappear as the force diminishes As a rule there is a transient blurring of vision as if a grey mist or veil were held before the eyes there may be a total loss of vision with consciousness retained (blacking out) In some pilots the process leading to the blackout may precipitate an acute loss of consciousness

The cause of these phenomena is an impairment of the retinal and cerebral blood flow by the action of centrifugal force on the blood column the blood becomes heavier the fall in cerebral blood pressure as compared to that of the blood in the aortic arch is correspondingly increased the tendency for blood to accumulate in the splanchnic bed leads to a decrease in venous return which lowers cardiac output

As a rule normal persons in good physical condition are capable of withstanding the centrifugal forces developed in modern aircraft On the other hand any intrinsic vascular weakness however slight increases the susceptibility to the circulatory changes produced by centrifugal force Persons who show a tendency to faint on sudden change in posture are unfitted for qualification as airplane pilots

SYNCOPE DUE TO HIGH ALTITUDES

The fall in oxygen content and oxygen partial pressure at altitudes above 10 000 feet leads to *altitude sickness* The degree of anoxemia depends on the altitude and on the oxygen requirements of the tissues

Altitude sickness produces increased rapidity of pulse and respiratory rates headache, lassitude euphoria nausea and vomiting usually in that order Forward failure (p 941) may supervene unless oxygen therapy is prompt and effective

The cause of the circulatory collapse probably resides in anoxemia of the vasomotor center and widespread dilatation of the capillaries in the muscles in response to oxygen lack The tendency to acute circulatory collapse at high altitude is enhanced by the action of centrifugal force (p 925)

SYNCOPE DUE TO SYSTEMIC CAUSE

A variety of systemic disturbances predispose to syncope These include *malnutrition exhaustion generalized arteriosclerosis cachexia* and *pregnancy* According to those who write our plays novels and scenario the fainting attack seems as reliable a physical sign of pregnancy as the rabbit test

Differential Diagnosis —The problem in the differential diagnosis of syncope involves (1) the exclusion of the presence of other clinical syndromes, and (2) after establishment of the fact that the attack is one of a fainting spell an elucidation of the provocative or precipitating mechanisms

Epilepsy —There may be considerable difficulty in differentiating repeated attacks of syncope and epileptic seizures Table 55 summarizes the more useful clinical data

Hypoglycemic Shock —Hypoglycemic shock may be associated with loss of consciousness under which circumstance it closely resembles an attack of fainting The clinical features which suggest the derangement in the metabolism of blood sugar include a history of insulin injections in

that follow upon the use of these substances is psychogenic rather than pharmacologic

PULMONARY HYPERTENSION (HYPERTENSION OF THE LESSER CIRCULATION) WITH COR PULMONALE

Pulmonary hypertension is dependent upon mitral stenosis (p 970) pulmonary arteriosclerosis or chronic obstructive lesions of the respiratory organs Illustrative of the latter are such diverse clinical entities as *emphysema* (p 2056) *bronchiectasis* (p 2059) *extensive tuberculosis* (p 2199) *thoracic deformities* (p 2046) *bronchial asthma* and *chronic passive congestion of the lungs*

Clinical Manifestations—The diagnosis of pulmonary hypertension can only be suspected before autopsy The *primary symptoms* include dyspnea cough vertigo hemoptysis and precordial pain venous pressure may be increased the superficial veins may be engorged the second pulmonic sound may be accentuated the silhouette of the heart suggests dilatation and hypertrophy of the right side with prominence of the pulmonary segment the *electrocardiogram* exhibits a right axis deviation These changes may be associated with cyanosis and enlargement of the liver *Roentgenograms* aside from the changes in the conformation of the heart reveal increased pulmonary markings or evidences of actual disease (Fig 124)

Ayerza s Disease—Ayerza s disease is probably an example of pulmonary hypertension with advanced *cyanosis* and *polycythemia* (p 1092) See also *Geisboeck s Disease and Osler Vaquez Syndrome* (p 1093) with albuminuria and cardiac failure

Treatment—The present treatment of pulmonary hypertension is limited to palliative measures Frequent phlebotomies may be of some utility particularly in the presence of increased blood viscosity and polycythemia (p 3,80)

PORTAL HYPERTENSION

See p 710 and p 1960

OBSTRUCTION OF VENAE CAVAE

See p 710

ARTERIOVENOUS FISTULAE

See p 711

culatory phenomena of *acute inflammation* (p 16) Capillary and venous channels are widened the vascular bed is enlarged and there is evidence of capillary stasis and interstitial edema The chief differences between the two phenomena are the widespread distribution and the diminished tissue metabolism in shock

The vascular phenomena in shock are very similar to those seen as the result of skin injuries which result in the triple response and the production of the wheal This analogy has led physiologists to assume that a *histamine like substance* is produced as the result of shock this product in its turn creates a vicious cycle by increasing capillary dilatation and favoring the extravasation of fluid from the vascular bed to the extra vascular compartments

TABLE 6—DIAGRAMMATIC REPRESENTATION OF THE CYCLIC NATURE OF THE VASCULAR FAILURE IN SHOCK

Reduced Venous Return ⟶ *Reduced Cardiac Output*
Vasoconstriction
Capillary Stasis
Decreased Blood Volume { Hemorrhage, Transudation, Dehydration
Anoxemia
Toxic Substance
Increased Capacity of Vascular Bed
Increased Capillary Permeability
Capillary Dilatation
Arteriolar Dilatation ⟵ *Vasomotor Failure* ⟵ *Tissue Anoxia*

In shock the superficial veins are bloodless while the blood in the heart great vessels and the parenchyma of the organs is dark thick and incoagulable The serous membranes particularly of the abdominal cavity are congested and covered with ecchymoses the serous cavities often contain blood tinged fluid The mucosa of the gastro intestinal tract is congested edematous and ecchymotic and small acute ulcerations may be present in any portion of the digestive system The lungs are i regularly congested liver and kidneys are cyanotic and their cut surfaces drip blood the heart is cyanotic and its veins and capillaries are engorged the spleen is often small and relatively bloodless hemorrhages are noted in the adrenals

Microscopic examination of the tissues reveals distention of the capillaries edema of the interstitial tissues and frequent areas of hemorrhage The parenchymal cells show evidences of acute cloudy swelling (p 7)

Etiology—The discussion of pathogenesis emphasizes the fact that the

tations were merely those of hypotension and fatigue Patients should be asked to bring urine and stool specimens for routine analysis The fever curve should be charted for several days A hemogram and a chest x ray are essential constituents of the survey and if nothing else is disclosed the infrequent Addisonian syndrome should be considered

If psychogenic and organic disturbances can be eliminated and the hypotension and fatigue appear to be mere functional disturbances the patient may be advised to take a partial or complete rest cure (p 8754)

DIFFERENTIAL DIAGNOSIS OF

Blood Pressure Anomalies Other Than Those Related to Systolic Tension

Besides alterations in systolic tension the clinician may obtain information from changes observed in diastolic and pulse pressures and from differential pressures in arms and leg

FINDING	DIFFERENTIAL FEATURES
Increased Diastolic Pressure	From persistence of causes of systolic hypertension (p 910)
Diminution of Diastolic Pressure	In association with systolic hypotension but also in aortic insufficiency (p 970) and hyperthyroidism (p 1197)
Increased Pulse Pressure	Particularly in aortic insufficiency (water hammer pulse) hyperthyroidism, complete heart block and neurocirculatory asthenia Listen for aortic diastolic murmur Get B M R and Ecg
Diminution in Pulse Pressure	With backward failure (p 941) when systolic tension falls and diastolic rise In aortic stenosis (plateau pulse)
Differences Between the Two Arms	With scalenus anticus syndrome cervical rib aortic aneurysm and occlusion of brachial, axillary or subclavian arteries Get x rays of cervical spine and chest
Abnormal Differences Between Arms and Legs	Relative hypotension in legs with coarctation of aorta and embolization or thrombosis of bifurcation
Differences Between the Two Legs	From peripheral vascular disease particularly arteriosclerosis and thrombo-angiitis obliterans From thrombosis or embolization of iliac femoral or popliteal vessels

Symptomatic therapy may be attempted with sodium chloride given in capsules of 0.5 gm (7½ grains) five or six times daily These may be supplemented by easily available sugar in the form of candy carbonated drinks or ice cream soda We do not approve of injections of potent extracts such as desoxycorticosterone or other adrenal cortical preparations unless there is more than a mere suspicion of the Addisonian syndrome Perhaps the most popular injection therapy for asthenia and hypotension is the so called neurasthenic serum which is a weak solution of cacodylate of soda and neurophosphates In our experience any beneficial results

4 Note the presence of aortic and/or mitral stenosis (p 970)
5 Take an electrocardiogram for evidences of coronary insufficiency or thrombosis (pp 895 983)
6 Do a hemogram for evidences of anemia or polycythemia (p 3692)
7 Seek evidences of concealed hemorrhage, particularly by stool examination
8 Seek evidences of pregnancy

Treatment—The immediate treatment of the syncopal attack is outlined elsewhere in the description of the management of vasovagal episodes (p 922) Depending upon the etiologic factors other therapeutic measures include intravenous injection of atropine sulfate when the attack follows the use of a choline derivative transfusion in an anemia, phlebotomy in a polycythemia quinidine for a paroxysmal cardiac irregularity (p 873) atropine amphetamine paredrine or ephedrine in carotid sinus attacks with surgical interference if symptomatic medication is not effective

SHOCK

Shock is the clinical syndrome produced by peripheral failure of the circulation the defect resides in the vascular mechanisms that are involved in the distribution of blood to the tissues and its subsequent return to the heart The circulatory breakdown results in widespread tissue anoxia and a general depression of all vital functions

Shock and Syncope—The chief differences between syncope (p 921) and shock are the greater intensity of the defect in the latter and its relative irreversibility In syncope the circulation fails acutely the breakdown is transitory it is easily remedied and its effect is almost wholly upon cerebral blood flow In shock the failure usually develops insidiously it is more widespread the injury is more profound hemoconcentration is produced the capillaries are severely damaged spontaneous recovery is less frequently noted and active treatment is required often as a life saving measure

Pathogenesis—Irrespective of its cause and precipitating factors the shock syndrome is characterized by a *diminished return of venous blood* from the periphery to the heart The decrease in effective circulating blood may be produced by an actual reduction in its volume as the result of loss of fluid and salt from the body its escape into the extravascular compartments increase in the surface area of the vascular bed due to venous and capillary dilatation

Local anoxia leads to attempts at compensatory *vasoconstriction* and the production of toxic substances resembling *histamine* (p 3890) The latter increase capillary dilatation and capillary permeability creating a vicious cycle

The central effects of the shock syndrome include a subnormal venous return to the heart a decrease in its diastolic volume and a progressive fall in cardiac output The total of this progressively unfavorable sequence is a local anoxia with depression of all tissue functions The effects are most clearly shown by depression of the central nervous system impairment of kidney function weakening of the myocardium collapse of the peripheral veins and fall in venous pressure

Pathology—The pathologic changes produced in shock resemble the cir

SYNCOPE

The attack of fainting consists of an acute and transitory loss of consciousness The incident is attended by a temporary depression of all vital activity In most instances the fundamental cause is a cerebral ischemia which may be neurocirculatory hemic circulatory or of systemic origin Rapid recovery from syncope is the usual experience though an occasional attack may prove to be fatal Syncope differs from shock only in its lesser intensity and shorter duration

Pathologic Physiology—The most frequent fundamental cause of syncope is circulatory insufficiency leading to cerebral ischemia less often the attack is due to cerebral engorgement

The mechanisms responsible for the reduced cerebral circulation may be *central* (*cardiac*) or peripheral in the former the cardiac output falls because of an abnormality of the heart itself in the *peripheral* group there is a reduction in venous return and a corresponding fall in cardiac output In some instances both mechanisms may be operative

Clinical Manifestations—The syncopal seizure varies in its finer details with the mechanism of causation but there are certain characteristic findings common to all types The actual seizure may be preceded by a short *aura* of impending dissolution (angor animi) if the degree of cerebral anemia is mild the patient complains only of weakness dizziness lightheadedness dimness of vision scotomas nausea or vomiting The premonitory symptoms may prompt the patient to lie down aborting the actual syncope but more often the onset is followed quickly by loss of consciousness and falling to the ground In some instances however there may be no warning symptoms but merely the sudden occurrence of unconsciousness

The unconscious patient appears pale and is covered with beads of cold sweat the pupils are widely dilated the corneal reflexes are sluggish or absent respirations are usually slow and shallow but may be deep and sighing Unless the attack has been precipitated by some cardiac abnormality the heart rate is slow and the sounds are poor the radial pulse is soft and barely perceptible there may be slow clonic movements of the muscles of the face and upper extremities generalized epileptiform convulsions are not uncommon

As a rule the unconscious period lasts but a few seconds but it may persist for several minutes recovery is gradual and may be attended by nausea vomiting profuse sweating involuntary micturition and defecation The patient usually remains weak pale and perspiring for one half to one hour after the return of consciousness

The tendency to syncope is enhanced by cerebral arteriosclerosis anemia and anoxemia Gravity tends to accentuate the intensity of the circulatory collapse fainting rarely occurs while the patient is recumbent but epileptic seizures are frequent in this position

Vasovagal Syncope—Vasovagal syncope is the term that designates the common fainting attack which occurs as the result of a neurocirculatory disturbance The episode may occur in a patient who is apparently healthy but is more apt to be encountered in those who are in poor physical condition Certain individuals have a tendency to faint on slight provocation while others are relatively immune

ETIOLOGY—The fainting attack may be precipitated by any one of a

Clinical Manifestations—The recognition of the fully developed clinical picture of shock presents no clinical problem Unfortunately by the time the full blown syndrome becomes apparent many of the pathologic changes are irreversible and hence present a formidable problem for the therapist The early recognition of impending shock is the problem to which the astute practitioner must apply himself To accomplish this he requires keen observation and laboratory assistance for his acumen the patient will be rewarded by a prompt response to the early initiation of the indicated therapeutic measures

Impending Shock—The diagnosis of impending shock is suggested by findings which do not require the utilization of any unusual apparatus The observant physician notes a change in the appearance of his patient who becomes pale pinched anxious and somewhat sweaty The rectal temperature tends to fall the pulse rate rises urinary output diminishes repeated blood pressure readings reveal a fall in the systolic level a decrease in pulse pressure and relatively slight alteration in the diastolic level

If it is at all possible laboratory assistance is invoked at this time The characteristic changes include increases in the hemoglobin concentration the erythrocyte count and the hematocrit readings a rise in plasma specific gravity and a fall in plasma volume

Fully Developed Shock—The clinical picture of fully developed shock presents an alarming and indelible appearance The patient is apathetic and almost oblivious to external stimuli responses are slow and often difficult to elicit and consciousness is dulled although an occasional patient appears alert and communicative restless excitable and even delirious The skin is pale and moist cold and clammy the characteristic *hippocratic facies* is marked by sunken eyes a grayish pallor and prominence of the tip of the nose which gleams with drops of sweat The extremities are cyanotic and mottled cutis marmorata may be present the superficial veins are collapsed and venipuncture is difficult The respiratory rate is rapid but the excursions are shallow and sighing some patients exhibit a slow and superficial type of respiration but others have hyperpnea of the Kussmaul type of Cheyne Stokes breathing The *pulse* is rapid small and easily compressible the level of blood pressure usually is less than 80 mm of mercury in the systolic reading with an imperceptible diastolic level the pulse pressure is usually decreased Exceptionally the *blood pressure* remains normal for many hours despite other unmistakable evidences of shock *Heart sounds* are usually distant and faint they have the quality of an embryocardia with tic tac rhythm the heart is small and with progressive weakening of the myocardium a gallop rhythm may be made out

The *central nervous system* is depressed the patient is usually stuporous and difficult to arouse the pain sense is dulled consciousness is retained until shock deepens when coma supervenes just before the fatal issue The *pupils* are usually widely dilated with a sluggish reaction to light the corneal reflexes are depressed Superficial and deep *tendon reflexes* are difficult to elicit the muscles are lax flaccid and almost devoid of tonus muscle twitchings are often observed and a coar e tremor may be present Muscle strength is startlingly weakened and the raised limb falls heavily as if it were in the state of a flaccid paralysis

CHAPTER 41

PHYSIOLOGICAL DISTURBANCES OF THE CIRCULATORY SYSTEM CIRCULATORY DEFICIENCY FORWARD FAILURE SHOCK

Circulatory Deficiency
Forward Failure
Syncope
Shock

CIRCULATORY DEFICIENCY

In this presentation the term 'circulatory deficiency is used in preference to cardiac failure ' cardiac deficiency' or 'congestive failure The term *circulatory* is preferred to cardiac' since the clinical abnormality involves more than a mere disturbance of the heart, *deficiency* is used rather than failure because of its lesser sense of finality

The vital problem that concerns the practitioner in the management of any circulatory abnormality is the *maintenance of efficiency* The patient may have a damaged heart valve sclerosed vessels and varicose veins but so long as his circulation is adequately maintained he is physiologically solvent His condition is much like that of a business concern which records a varying number of losing transactions but satisfactory annual earnings in the final balance sheet

In his effort to maintain or reestablish circulatory efficiency the practioner recognizes many powerful allies The circulatory system has a wide margin of safety its integrations are delicately attuned compensatory mechanisms are rapidly called into play and many potent therapeutic agencies are readily available However, there are limits even to the reserve power of the circulatory mechanism deficiencies are inevitably encountered despite all efforts of the body to maintain an adequate flow of well oxygenated blood to vital tissues The problems of the failing circulation are the present concern and the recognized varieties include forward and backward failure

Forward failure is essentially a tissue anoxia it is seen in an acute transitory form in syncope more protracted examples constitute the state of shock

Backward failure (p 941) is usually referred to as 'congestive heart failure or chronic passive congestion' The fundamental defect is essentially central and the failure of the tissues to be properly oxygenated results from inability of the pump to maintain an adequate velocity of blood flow (p 774) or the required volume output

FORWARD FAILURE

The syndromes of forward failure include the transitory attacks of fainting and the more protracted manifestations of shock

precipitating factors in the development of shock include a reduction in circulating blood volume or an increase in the volume capacity of the vascular system The following table lists more specifically the clinical circumstances that may lead to either of the provocative physiological derangements

TABLE 57—THE ETIOLOGY OF SHOCK

Reduction in Circulating Blood Volume
- *Loss of Body Fluid*
  - From the Gastro intestinal Tract
    - Persistent Vomiting
      - *Pyloric Obstruction*
      - *Acute Gastric Dilatation*
      - *Intestinal Obstruction*
    - Persistent Diarrhea
      - *Cholera Infantum*
      - *Acute Enteritis*
      - *Acute Dysenteries*
      - *Chronic Ulcerative Colitis*
      - *Asiatic Cholera*
    - External Intestinal or Biliary Fistulas
  - From the Body Surface
    - Burns
    - Weeping Skin Lesions
  - From the Urinary Tract
    - Adrenal Insufficiency
    - Diabetic Acidosis
    - Excessive Diuresis Produced by Drugs
  - External Hemorrhage (Hematogenic)
- Extravascular Escape of Body Fluid (Vasogenic)
  - Through Damaged Capillaries
    - Traumatic Shock
    - Acute Infections
    - Burns
    - Chemical Shock
    - Diabetic Acidosis
  - Redistribution of Fluids and Electrolytes
    - Adrenal Insufficiency
  - Internal Hemorrhage

Increase in the Volume Capacity of the Vascular System
- Acute Arteriolar Dilatation (Neurogenic Shock)
  - Severe Pain (Acute Pancreatitis)
  - Coronary Thrombosis (Cardiogenic)
  - Operative and Postoperative Shock
  - Vasomotor Failure
- Capillary Dilatation
  - Traumatic Shock
  - Chemical Shock (Histamine Shock)
  - Anaphylactic Shock
  - Toxic Shock (Snake Venoms Peptone etc)

Attention is drawn to the fact that a single lesion may invoke the operation of several different provocative mechanisms For example *diabetic acidosis* is accompanied by loss of fluid through the urinary tract and extravascular escape of body fluids through damaged capillaries *traumatic shock* results in extravascular escape of body fluids through damaged capillaries and increase in the volume capacity of the vascular system through capillary dilatation

wearing of a tight collar pressure from a calcified lymph node of the neck irritation by an adjacent tumor or a sudden twisting of the neck Less often the precipitating factors are distant and include such circumstances as the distention of a hollow viscus or increase in the excitability of the sinus by drugs such as digitalis

The cause for carotid sinus hypersensitivity usually is unknown abnormal reactivity is more common in elderly arteriosclerotics seizures occur more readily while the patient is in the erect posture and some instances seem associated with an orthostatic hypotension (p 916)

Varieties —Three distinct varieties of reflex response are recognized in carotid sinus syncope In the *vagal type* there is a marked cardiac response resulting in asystole in the *vasodepressor variety* there is widespread peripheral vasodilatation with pooling of blood in the splanchnic area the central type of syncopal response is probably a cerebral ischemia and it may be unattended by demonstrable changes in the pulse rate or blood pressure

Treatment —The attack of carotid sinus syncope is rarely observed by the physician whose efforts are mainly directed at preventive measures In the vagal type of syncope attacks may be lessened by daily administration of *atropine sulfate* in doses of 1 to 0.5 mg (1/60 to 1/120 grain) The atropine effect is enhanced by the simultaneous use of *ephedrine* (p 3880) in 25 mg (3/8 gr) dosage or paredrine 40 to 60 mg (2/3 to 1 grain) may be tried In the vasodepressor type of syncope ephedrine is of greater value than atropine though both drugs again may be combined In the cerebral types of syncope neither drug is of great value

Those patients who have frequent attacks and whose sinus sensitivity is demonstrably unilateral may be subjected to *surgical section* of the carotid sinus nerve or denervation of the vessel wall Bilateral operative interference creates the theoretical hazard of producing an arterial hypertension such as occurs in experimental animals

OCULOVAGAL SYNCOPE

Firm pressure on the eyeballs may lead to such slowing of the heart as to produce a syncopal attack there is little accompanying fall in blood pressure until actual loss of consciousness has occurred

Oculovagal syncope rarely occurs spontaneously it is encountered when the maneuver is attempted in the effort to relieve a *paroxysmal cardiac irregularity* (p 873) Occasional instances have been observed with hemorrhage and tumors of the orbit (p 1615)

SYNCOPE OF HEMIC ORIGIN

Attacks of syncope are seen in *anemia* (p 1055) and in *polycythemia* (p 1092) In the first instance the fainting attack is due to anoxia it is more apt to follow an acute hemorrhage of internal origin than a slowly progressive decrease in the numbers of the circulating red cells

Attacks of fainting are also seen in those who suffer from *polycythemia vera* (p 1093) These patients often complain of transitory attacks of vertigo with blurring of vision weakness and loss of consciousness the difficulty is due to slowing of the cerebral circulation from increase in blood viscosity Plethoric individuals often faint following dietary or alcoholic

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number of provocative circumstances These may include an emotional upset fright fatigue loss of sleep, vomiting straining at stool or the cramps of painful menstruation (p 2561) or of urgent defecation Syncope may be associated with instrumentation such as catheterization or the puncture of a vein it often is associated with needling of a serous cavity such as the pleura the peritoneum or the pericardium it can follow a simple hypodermic injection or a minor surgical procedure Even the sight of blood or exposure to any unpleasant or undesirable circumstance suffices in the susceptible

Fainting attacks are occasionally associated with intense pain such as a colic angina (p 890) or the perforation of a hollow viscus as in peptic ulcer (p 1790)

PATHOGENESIS —No matter what the precipitating factor the essential mechanism of vasovagal syncope is a decrease in the venous return to the heart resulting from widespread peripheral vasodilatation and pooling of blood in the splanchnic area The cardiac slowing is vagal in origin and contributes to the general physiologic derangement

TREATMENT —Vasovagal syncope rarely requires treatment since consciousness has usually returned by the time the physician puts in his appearance Should the incident occur during the course of an examination or the performance of a therapeutic procedure it is necessary only to place the victim in the horizontal position loosen the clothes and apply abdominal compression The fainting attack may be prevented by the inhalation of ammonia and by squeezing or straining as at stool

Fainting attacks that occur in the absence of the physician are usually complicated by the well intended therapy of anxious bystanders More often than not a drink of whiskey is forced down the victim s throat cold water has been splashed in every direction and household ammonia has been applied in sufficient strength to cause local burns Occasionally a particularly strong armed first aider in possession of a hypodermic syringe injects the alleged stimulants including caffeine camphor coramine metrazol strychnine epinephrine or digitalis

Following recovery from the fainting attack, the patient is instructed to report to the office for a complete physical examination to detect the presence of any contributing or precipitating difficulty should one such be uncovered therapy is directed at the relief or elimination of this factor Patients with a tendency to syncope should be prepared with a dose of barbiturate or opiate before attempting any injection aspiration or operative procedure

CAROTID SINUS SYNCOPE

The carotid sinus is situated in the carotid bulb at the bifurcation of the common carotid artery It is sensitive to chemical and mechanical stimuli A fall in blood pressure within the vessel produces a reflex vasoconstriction and cardiac acceleration, a rise in blood pressure within the artery is attended by vasodilatation and bradycardia

In certain individuals an abnormal degree of sensitivity to mechanical pressure is present within the carotid sinus As a result seemingly inconsequential external pressure produces sufficient vasodilatation and bradycardia to result in an attack of syncope often in association with a mild convulsive seizure The provocative circumstances — be the

The *body temperature* is lowered and may reach 95° F In some instances skin and oral temperatures are lowered while the rectal temperature remains elevated or normal

The *blood findings* present the same qualitative alterations as previously noted (p 931) the quantitative changes become progressively more marked the blood levels of urea and nonprotein nitrogen increase total base falls serum potassium concentrations are high and serum sodium and chloride levels are depressed, the carbon *dioxide content decreases* *Urine volume* is scant and there may be complete anuria with failure of glomerular filtration when the blood pressure level falls below 70 mm of mercury Urine specific gravity is usually high but may be low and fixed despite the oliguria the urine often contains albumin casts and red blood cells

Shock Due to Loss of Body Fluids—With loss of body fluid (p 704) the clinical picture of shock is augmented by evidences of *dehydration* The tongue and mucous membranes are dry the eyeballs are sunken and soft, the fontanelle is depressed in the newborn, skin turgor is poor so *that skin folds persist after pinching hemoconcentration is more pronounced* there is greater nitrogen retention chloride depletion and reduction in plasma volume

Traumatic Shock—Shock is a major cause for death in all injuries and in many surgical procedures It develops most frequently after multiple *wounds with deep lacerations and with comminuted fractures*

PRIMARY SHOCK —When the peripheral circulatory failure develops immediately after the imposition of trauma it is known as primary shock Actually this prompt type of reaction is analogous to a *vasovagal syncope* (p 921) its manifestations and treatment are similar to those of *the attack of fainting*

TRUE TRAUMATIC SHOCK —True traumatic shock usually appears within four to twenty four hours after the injury it may develop early with wounds that involve the abdominal viscera Traumatic shock is much more serious in its implications than the initial primary variety It is *more apt to be encountered in those who have been exposed to* provocative circumstances such as starvation thirst extreme cold profuse sweating exhaustion pain fear prolonged anesthesia exposure of tissue rough manipulation during the course of the operative procedure or undue loss of blood

The clinical picture of true traumatic shock is that of a severe circulatory failure, the patient is apathetic ashen cyanosed and clammy Experimental investigations indicate that in many forms of trauma there is a marked loss of plasma and whole blood into the injured area with resultant decrease in circulating blood volume The latent period between time of injury and onset of shock may be the interval required for sufficient blood or plasma to pass from the vascular tree to the traumatized area The attempted compensatory vasoconstriction further diminishes venous return to the heart and increases the physiological derangement which is made worse by the well intentioned administration of epinephrine

Burn Shock—Following a severe burn the most important cause of death is shock it is most apt to occur when large areas of the body surface are involved As in traumatic shock, the burned patient first suffers

a possibility of a fatal termination unless the cardiac beat can be initiated by mechanical massage (p 3779) or injections of epinephrine given intravenously intra arterially or intraventricularly

SYNCOPE DUE TO ORTHOSTATIC CIRCULATORY INSUFFICIENCY (GRAVITATION SHOCK)

In the normal individual change in posture from the horizontal to vertical is attended by an increase in peripheral vasoconstriction acceleration of the heart and increased tonus in the skeletal musculature These adjustments counteract the effects of gravity on the blood column they insure an equable distribution of blood in the erect posture Impairment of the capacity of the vascular structure to adapt itself to these changes favors the stasis of blood in dependent venous areas there is a reduction in venous return and the onset of cerebral anemia leading to vertigo and syncope

Etiology —Orthostatic circulatory insufficiency is observed most often in the *convalescent patient* who has been invalided for a considerable period of time and is attempting to resume normal activities it occurs also in patients with *hypotension* (p 916) who have lost considerable weight it may be a manifestation of *neurocirculatory asthenia* (p 897) it may follow prolonged periods of standing at attention or the excessive strain of exercise as in heated athletic competition or prolonged military drill It is a postoperative complication of *splanchnicectomy* for *hypertension* (p 914) it is noted in neuromuscular disorders such as *tabes dorsalis* (p 1464) *syringomyelia* (p 1505) and *myasthenia gravis* (p 2880) and it occurs also in *Addison's disease* (p 1271) *Simmonds disease* (p 897) and *multiple avitaminoses* (p 616)

Clinical Manifestations.—The clinical manifestations of orthostatic circulatory insufficiency are clearcut The patient notes weakness vertigo dimness of vision or syncope when rising from the recumbent position The disturbance is less severe following exercise and may be relieved by the assumption of a horizontal position Estimations of blood pressure taken while the patient is reclining and then erect reveal a considerable fall when the upright position is assumed

Gravitational shock may be associated with cardiac acceleration and/or hypotension carotid sinus hypersensitivity also may be present Evidences of sweat gland hypofunction are fairly common suggesting some disturbance in the realm of the involuntary nervous system

Treatment.—Orthostatic circulatory insufficiency is best treated by graded exercises (p 3756) *resting in a head up bed* and the use of an abdominal binder and *leg bandages* Drug therapy includes the use of *amphetamine sulfate* (p 3869) in 5 to 10 mg ($\frac{1}{12}$ to $\frac{1}{6}$ gr) dosages or *ephedrine* in 25 mg ($\frac{3}{8}$ gr) doses The administration of *adrenal cortical extract* (p 1267) is not consistently helpful but may show an occasional extraordinary effect

SYNCOPE DUE TO CENTRIFUGAL FORCE (CENTRIFUGAL SHOCK)

Visual disturbances (blurring grey veil blacking out) and syncope are commonly experienced by *airplane pilots* as a result of the action of centrifugal force during *power dives* and in *air combat* when the plane is continually changing its direction

from a primary and acute *circulatory failure* which resembles vasovagal syncope and is probably due to the intensity of the pain and the contact of the burned surfaces with colder air After a latent period of several to forty eight hours the manifestations of the more serious physiological derangement are encountered venous return to the heart has been diminished due to local loss of the plasma into the burned area where the injury has produced capillary dilatation and increased capillary permeability

The local loss of fluid in extensive burns may approximate 70 per cent of plasma volume the extravasated fluid has a high protein content and is very similar to plasma in its chemical composition The local circulatory derangements are not limited to the traumatized area but appear to be widespread the toxin formed in the burned area probably gains access to the circulation and produces widespread capillary damage and toxemia Additional factors that tend to perpetuate and increase the clinical derangement are hyperpotassemia and possible adrenal cortical insufficiency since bilateral hemorrhages are often seen in the severely burned

Shock in the Acute Infections—In many of the acute infections failure of the peripheral circulation is a common and extremely serious complication It often occurs terminally and is perhaps a most frequent immediate cause for death The acute infections that are attended by peripheral circulatory failure have in common an extreme degree of toxemia The vascular failure is probably a result of the action of toxins on the capillary bed and the vasomotor center (vasomotor paralysis)

In clinical practice peripheral circulatory failure was most often seen in *lobar pneumonia* (p 2171) in the pre-sulfonamide era The complication might occur at the height of the infectious process but also was encountered at or following the crisis In the great *influenza* epidemic of 1917 1918 peripheral circulatory failure was very frequently encountered its severity was great there was marked hemoconcentration probably due to diffuse capillary injury as the result of the toxicity of the pathogenic organism blood volume was considerably reduced also by the early and widespread hemorrhagic pulmonary edema (p 943)

In *diphtheria* (p 302) circulatory failure results from cardiac and peripheral damage The bacterial toxin which injures the myocardium also is noxious to capillaries The onset of difficulty is often gradual but occasionally may be so acute as to suggest a pulmonary embolization (p 2096) Similar experiences are noted in *typhoid fever* (p 225) *gangrene* (p 3990) and *cholera* (p 249) In the last the loss of fluid and salt through diarrhea contributes appreciably to the toxic factor in the circulatory collapse

In Adrenal Cortical Insufficiency—The crisis in Addison s disease (p 1275) presents all of the clinical manifestations of forward failure At times the onset is gradual following several days of extreme weakness anorexia vertigo and evidences of orthostatic hypotension In other instances the development is acute as the result of inadequate therapy the onset of a superimposed acute infection an emotional upset or a surgical procedure

The mechanism of shock in adrenal insufficiency is complex it involves excessive *loss of sodium and water* in the urine the tendency for these elements to leave the extracellular compartment and enter the cells the resultant reduction in circulating *plasma volume* retention of *potassium* in the serum and possible loss of adrenal cortical control in the mainte-

indiscretion particularly when they are in an overheated room Often the immediate provocative circumstance is a lowering of the head as in picking some object up from the floor In these instances it is likely that there is an increased venous pressure in the circulation with sufficient stasis to prevent adequate oxygenation of the tissue

Treatment —The treatment of syncope due to anemia requires hemostasis and blood transfusion (p 3779), the same complaint in the polycythemic or the plethoric may be benefited by a generous phlebotomy (p 3780)

SYNCOPE OF CIRCULATORY ORIGIN

Syncope due to circulatory disorders may be central or peripheral in origin The central causes for syncope are usually related to a diminished volume output from the ventricles as in acute coronary insufficiency (p 983) acute coronary closure (p 983), at the beginning of a paroxysm of cardiac arrhythmia (p 873) with valvulitis, and particularly aortic and mitral stenosis resulting in an inadequate ejection of blood with each ventricular systole

The peripheral causes for fainting of circulatory origin are usually related to hypotension and vasodilatation Illustrative of the former are the attacks that occur in Addison s disease (p 1271), the more striking examples of syncope due to vasodilatation are noted when patients are given nitroglycerin (p 3893) or a choline derivative (p 3874) Drug syncope is more apt to occur if the preparation is administered while the person is in the erect posture, patients with angina (p 890) for example are warned to recline before taking their therapeutic tablet or inhalation

The less common circulatory causes for attacks of syncope include episodes of cerebral ischemia observed in *backward failure* (p 941) with extreme reduction in cardiac output and those which are encountered in *neurocirculatory asthenia* (p 897)

Treatment —The treatment of the circulatory types of syncope is directed at the more fundamental cause

SPEED SHOCK

The syndrome of speed shocks occurs when any extraneous substance is rapidly injected by the intravenous route The condition is similar to if not identical with, the *nitritoid crisis* or the *anaphylactoid reaction* It is not due to the nature of the injected substance but to a technical error which is easily prevented by slow introduction of the intended therapeutic agent (see p 3774)

NITRITOID CRISIS

The nitritoid crisis which is most likely an example of speed shock is encountered with intravenous injections of the *arsphenamines* (p 116) The patient suddenly develops cough precordial oppression vomiting pallor and loss of consciousness blood pressure falls and the radial pulse may be imperceptible Recovery is rapid and may be speeded by the subcutaneous injection of 0.5 to 1 0 cc of 1 1000 epinephrine hydrochloride

SYNCOPE IN THE STOKES ADAMS SYNDROME

Syncope occurs when there is total *heart block* as the result of a prolonged period of ventricular asystole Under these circumstances there is

nance of normal capillary permeability and volume Often the *Addisonian death* occurs with profound asthenia low blood pressure a small soft pulse peripheral cyanosis and a terminal hyperpyrexia In many of these examples there is apparently no relationship of the symptomatology to the state of electrolyte or water metabolism or to the blood sugar level Replacement therapy with adrenal cortical extract and desoxycorticosterone may be ineffectual

Shock in Diabetic Acidosis—In diabetic acidosis (p 1251) shock may occur as a herald or a fatal complication It may be encountered in acute or long continued acidosis and although it is usually seen in the adult it may occur with advanced coma in patients of any age

The condition of shock in diabetic acidosis is indicated by fall in systolic tension, hemoconcentration oliguria progressing to anuria elevation of the blood nonprotein nitrogen a deceptive decrease of glycosuria and disappearance of acetone bodies from the urine The paradoxical urinary phenomena are the result of renal block due to the failure of the kidney blood flow

The shock in diabetic acidosis is dependent upon a decrease in plasma volume an increased urinary output is needed to wash out the excess of acetone bodies and with the polyuria there is a renal loss of fixed base Widespread capillary damage results from the excessive retention of ketone bodies A negative fluid balance is established partially due to the hyperpnea which causes an appreciable loss of water through the lungs and the associated nausea and vomiting further deplete the body of fluids Often the importance of shock during acidosis is most clearly delineated by the persistence of the signs of forward failure after the metabolic derangement has been corrected by the administration of sodium chloride water and insulin

Shock in Hemorrhage—With large losses of blood the appearance of forward circulatory failure is due partially to *decrease in plasma volume* Hematogenic shock differs from other manifestations of shock in that there is *increased coagulability of the blood* Accessory factors which contribute to the shock syndrome include associated pain the attendant emotional disturbances and the presence of compensatory vasoconstriction intended to prevent the fall in blood pressure The latter aggravates the already existent tissue anoxia and leads to the production of more widespread capillary dilatation The vasomotor center exhibits the *Traube Hering waves* due to continued blood loss and alternating elevation and depression of arterial pressure In consequence blood pressure readings are not an accurate index to the state of the peripheral circulation and more information is obtained from studies of hemoconcentration

The importance of the element of peripheral circulatory failure is often exemplified by the persistence of the syndrome of shock after blood loss has been compensated by adequate transfusion

Shock Due to Neurocirculatory Disturbances—As in the instance of syncope (p 921) intense stimuli which produce simple attacks of fainting may by their continued presence result in manifestations of shock This is seen particularly in protracted colic a violent angina pectoris the perforation of a hollow viscus or an intense prolonged strain of whatever character

diabetics and in nondiabetics the complaint of voracious appetite and an inordinate craving for sweets The diagnostic problem is best solved by making blood sugar studies for several successive hours following the ingestion of a meal rich in dextrose (p 3714)

The Pathogenesis of the Syncopal Attack —Once the diagnosis of syncope has been established it is the practitioner s obligation to determine the provocative circumstance The history may reveal the immediate cause

TABLE 55 —A COMPARISON OF THE PRINCIPAL CLINICAL FEATURES OF SYNCOPE AND EPILEPSY (After Weiss)

Clinical Feature	Syncope	Epilepsy
Aura	Present	Present
Duration of aura	Short	Prolonged
Olfactory aura	Absent	Frequent
Loss of response with retained motor function	Absent	Present (petit mal)
Color of face	Pale	Pale then flushed
Convulsions	Mild	Severe
Tongue biting	Absent	Present
Perspiration	Cold	Warm
Heart	Slow or normal	Rapid
Respiration	Quiet and shallow	Stertorous and labored
Vomiting	Present	Present
Defecation	Present	Present
Micturition	Present	Present
Duration of attack	Transitory	May be prolonged
Confusion after attack	Rare	Frequent
Headache after attack	Mild	Severe
Amnesia	Present	Present
Electroencephalogram	Normal	Abnormal

and no further investigation is required unless the fainting attacks are repeated

Should the syncope occur without immediate provocative cause the following investigations are required for a complete diagnostic survey

1 Test the effects of pressure on the carotid sinus (p 922)
2 Note the blood pressures in the recumbent and erect positions (p 3486)
3 Observe the presence of any cardiac irregularity (p 873)

Shock Due to Circulatory Phenomena—The diminished cardiac out put that accompanies many circulatory lesions may result in the production of syncope (p 921) This is noted in *acute coronary insufficiency* (p 983) in *acute coronary closure* (p 983) at the onset of a *paroxysmal cardiac irregularity* (p 892) in orthostatic and other forms of *hypotension* (p 916) and with ventricular asystole as seen in *total heart block* (p 879)

The association of a diminished cardiac output with the factor of pain as in acute coronary thrombosis is a particularly unfortunate mechanism in the production of the shock syndrome At times shock is present at the onset of the occlusion and its manifestations may cloud the more fundamental provocative lesion again it may not be encountered until a considerable period after the onset of the cardiac accident when it appears as a late complication

Other cardiovascular accidents that are frequently attended by severe manifestations of peripheral circulatory failure are acute pulmonary embolism (p 2086) and acute mesenteric thrombosis (p 994) In all likelihood the syndrome is produced by a reflex mechanism resulting in a redistribution of blood

Shock Due to the Use of Drugs and Chemicals—A number of chemical substances many of which are employed with therapeutic purpose are capable of producing the syndrome of shock by one mechanism or another Thus the manifestations of peripheral circulatory failure are seen in *acute mercurial poisoning* (p 765) when there is marked loss of fluid through nausea vomiting and diarrhea and additionally widespread capillary damage the intravenous use of mercurials for diuretic purposes (p 2261) is occasionally followed by shock which may be due partially to fluid loss and partially to the syndrome of *speed shock* (p 936) Peripheral circulatory failure is seen in *lead poisoning* (p 762) it may be associated with the therapeutic injections of *gold salts* (p 2922) *the arsenicals* (p 116) and *antimony* (p 132)

In sensitized individuals the injection of a small amount of *cocaine* or the *cocaine substitutes* (p 3915) may produce an acute cardiovascular collapse which occasionally is fatal A more frequent type of peripheral circulatory failure associated with local anesthesia is that which is observed when the preparations are injected intrathecally (p 3917) In most instances of *spinal anesthesia* (p 3922) there is a fall of blood pressure due to paralysis of sympathetic vasomotor outflow resulting in a pooling of blood in the splanchnic bed and a reduction in the venous return For this reason most surgeons who employ spinal anesthesia utilize vasoconstrictor agents such as ephedrine in efforts to prevent and treat this disturbing complication

Inhalation anesthesia (p 3925) also is accompanied on occasions by peripheral circulatory failure At times the complication is due to the effect of the anesthetic agent which causes a central vasomotor depression with peripheral vascular injury In other instances the shock syndrome is a result of a combination of factors which include the trauma of operation the incidental loss of blood excessive concentration of the gas or a plane of anesthesia that is so light that the nervous system responds to all stimuli

be borne in mind Particularly in the enteric fevers such as typhoid the bed is to be screened Flies are kept out by screening the windows *Phenomenal progress has been made in the control of mosquito borne and other* vector disease by the use of DDT (p 3118)

While there is not yet absolute proof that the common cockroach transmits any of the important infectious diseases there is sufficient suspicion so that these pests should not be permitted to exist in the neighborhood of the patient Among the other nuisances of the sickroom may be included most visitors They should be treated as possible vectors

Contacts and Visitors —Visitors and members of the household as well as the nursing and medical staff are questioned concerning previous attacks of the disease or immunization Susceptible contacts must be protected wherever possible Immune contacts may be permitted to go about their business provided those in the household of the enteric fever patient are not food handlers The responsibility for allowing some members of the family to come and go while others must be quarantined rests upon the public health authorities

Care of the Body —The care of the body is similar in all infectious diseases Greater precautions are needed in debilitated and elderly patients and in the longer febrile disturbances such as typhoid fever The hygiene of the body includes a bed bath at least once and preferably twice daily The body is thoroughly dried and covered with talcum powder Special attention is given to drying in the creases of the body and on the points of pressure Febrile patients who perspire freely must have more frequent sponges

Care of the Skin —The skin may be well protected by frequent bathing drying and powdering If a point of pressure develops a decubitus sore may be prevented by the judicious use of pillows or a rubber ring Painting with Compound Tincture of Benzoin is also protective

Care of the Mouth —The hygiene of the mouth is of the greatest importance in patients who are receiving parenteral fluids Under these circumstances the mouth must be frequently rinsed to prevent a complicating parotitis Salivation is stimulated by the use of chewing gum

WATER INTAKE

The maintenance of an adequate water intake is essential in all febrile diseases This is assured by a urinary output of at least 1500 cc Sufficient fluids are administered orally to guarantee this output Should the output fall below the stated amount parenteral fluid may be administered if the patient cannot be coaxed into taking more It is important to ascertain that water retention is not responsible for the decreased urinary output Under this latter circumstance the forcing of fluids might lead to hydremia circulatory failure or water intoxication (p 705)

DIET

Dietary treatment is of little importance in the short fevers but in the long fevers the tissues and nutrition of the patient must be maintained Fortunately the day of starving fevers has long since passed

Most febrile patients should be given food in a form that is mechanically and metabolically simple Thus the diet should be fluid soft

chased two bridge tables or a strip of beaver board should be placed between the spring and the mattress The board should be cut so that approximately four inches of mattress are free at either end i e the beaver board is 8 inches shorter than the mattress

The mattress is covered with a rubber sheet since it is almost impossible to care for the patient and not spill soiled fluid Sooner or later this wetting causes a vile odor and the damp mattress produces maceration of the skin and eventual ulceration The rubber sheet is protected with a mattress cover over which the bed is made using linen sheets below and immediately above the patient

Blankets and coverlets are used according to need It is desirable to use a minimum of bed clothing Excessive amounts cause restlessness perspiration and unpleasant body odor

Urinal and Bed Pan —The patient must be taught the use of the urinal This is not always as simple as might appear Persistence is often necessary Bedpanning constitutes the greatest nuisance for patient and attendant The bedpan is warmed under hot water before use Rather than permit the patient to strain excessively a glycerine suppository a small enema of soapsuds and/or glycerine can be administered immediately before raising the patient onto the pan

Often it is wise if there is too much difficulty with pan and urinal to carry or assist the patient to the lavatory

Room Temperature —The temperature of the room is regulated to the patient s comfort but it is preferable to keep the room on the cool side Overheated rooms cause restlessness insomnia perspiration and add to headache and general discomfort *It is often difficult to persuade the laity* and even the nurses to permit the room to be cool so great is the fear of chilling

The room temperature should certainly never exceed 70° F The patient will be considerably more comfortable as a general rule if the temperature approaches 60° If chilling is complained of blankets may be added and a hot water bottle or an electric pad applied The patient will certainly sleep better feel better and cough less in a cool room the local sewing circle to the contrary notwithstanding

In excessively cold weather artificial heating is employed in the form of a fire stove or radiator In any instance measures are taken to keep the room moist as well as warm A pan of water is placed in the fireplace on the stove or on the radiator

Ventilation —Ventilation of the room is provided through the windows These should be opened top and bottom the amount varying with the inside and outside temperatures At least once a day the air of the room should be changed by throwing open both windows and doors while the patient is carefully covered up with a Turkish towel around the head

Most febrile patients prefer a darkened room so that blinds should be available During convalescence all available sunlight should be permitted to stream into the room the patient wearing sunglasses if necessary Many symptomatic disorders particularly insomnia anorexia restlessness and headache disappear when the bed is moved so that the light of day shines on the patient

Vectors —The possibility of animal transmission of disease must always

Shock is occasionally seen with the careless introduction of drugs which produce an acute lowering of blood pressure Thus it is seen after the administration of *histamine* (p 3890) which causes capillary dilatation and increased capillary permeability it occurs with *acetylcholine* under similar circumstances Histamine shock has particular theoretical importance since many investigators believe that it illustrates the possible causative agent in traumatic and anaphylactic shock The proponents of the histamine theory suggest that the substance is released as the result of tissue damage and produces vascular changes locally and systemically

Peripheral circulatory failure also accompanies excessive doses of drugs capable of producing acute elevation of blood pressure It is seen when high concentrations of *epinephrine* (p 3876) are injected intravenously or into the heart in some emergency, epinephrine increases the intense vasoconstriction that is present as part of the mechanism of shock and adds to capillary dilatation and the derangement in capillary permeability A quite similar type of reaction often accompanies the use of *posterior lobe pituitrin* (p 1179) particularly when the drug is given postpartum or in the effort to combat postoperative ileus (p 4010) or anuria (p 4018) In our experience the latter mishap is more frequently encountered than is generally recognized

Speed Shock —The syndrome of speed shock has been elsewhere discussed (p 924) This untoward happening is a nonspecific reaction which follows the excessively rapid intravenous introduction of even inert chemicals In most instances where an active pharmacological agent has been employed the symptomatology is regarded as a pharmacodynamic manifestation of the injected agent or as a type of idiosyncrasy With the *arsenicals* (p 116) it is described as the nitritoid reaction (p 122), with other substances it is sometimes regarded as an anaphylactoid reaction As in the syndrome of true traumatic shock an occasional fatality is encountered under which circumstance the pathological features include incoagulability of the blood

Speed shock is readily prevented by a slow intravenous injection using the syringe method or if large quantities of fluid are to be administered by the intravenous drip method

Shock in the Toxemias of Pregnancy —Peripheral circulatory failure is not uncommon following the delivery of patients who have *eclampsia* or the *preeclamptic states* (p 2638) The accident is favored by a prolonged labor excessive bleeding the sudden decompression of the abdominal cavity the effects of the anesthetic agent or of the too enthusiastic use of pituitary extracts following childbirth

Shock Due to Venoms —Snake bite bee stings and spider bites (p 3196) occasionally are followed by acute and severe peripheral circulatory failure The symptoms result from entry of the venom into the blood stream and may be prevented by ligation of the bitten area and the injection of antivenin (p 83) The basic mechanism for the development of shock as usual is sudden acute dilatation of the arterioles and capillaries

Allergic and Anaphylactic Shock —Acute anaphylactic or allergic shock (p 549) results from the effect of anaphylactoxin on the capillaries The intensity of the reaction may be mild but in more severe examples the complication is rapidly fatal

be obtained the accumulation is most often *right sided* resulting in a shifting of the heart and the mediastinal structures to the left or contra lateral side

The presence of a hydrothorax adds immeasurably to the anatomical difficulties under which the heart must operate The pulmonary alveolar surface area is diminished due to the factor of atelectasis, the heart displaced out of its normal position, functions at a disadvantage If the hydrothorax cannot be relieved by the simpler measures of therapy a *paracentesis* (p 852) is urgently demanded

Digestive Symptoms—*Anorexia nausea* and *vomiting* are early symptoms of right heart failure Often they are accompanied by *constipation* and increased difficulty with *hemorrhoids* Sensations of fulness and pain are noted in the *epigastrium* and *right hypochondrium* when there is intense hepatic engorgement there may be some accompanying *jaundice* as the result of impaired function of the congested liver and the destruction of blood associated with pulmonary infarctions

The congestive symptoms of the upper digestive tract are often confused with those produced by overenthusiastic use of *digitalis* (p 854) The use of the drug may seem contraindicated due to the similarity of the symptoms of congestive failure and those of digitalis intoxication Under these circumstances the patient may be deprived of the use of that agency which is most urgently required Conversely the symptoms of digitalis intoxication may be erroneously interpreted as the results of congestive failure under which circumstance the administration of the drug is continued to the misfortune of the sufferer

Ascites—A later manifestation of the process of edema formation is that in which there is free fluid within the peritoneal cavity To be recognized clinically a minimum of 500 cc of ascitic fluid is required The patient notes that the corset or belt appears tight there is seeming *distention* everything turns to gas the floating up of the intestines on the water bed gives a deceptive appearance of tympanites until *dulness* is noted in the flanks a shifting is observed in the lateral recumbent positions and later a *fluid wave is distinctly palpable*

Persistence of ascitic fluid despite adequate conservative therapy calls for the performance of an *abdominal paracentesis* (p 1920)

Cardiac Cirrhosis—Prolonged congestion of the liver may eventually lead to a cardiac cirrhosis with the manifestations of *portal obstruction* (p 1969) The presence of this complication is suggested when the liver fails to resume its normal size after decongestive therapy

Urinary Symptoms—An early manifestation of congestive failure is diminution in urine output Often the *oliguria* is associated with *albuminuria* (p 3672) *cylindruria* (p 3683) and *hematuria* (p 2306) the latter observed only on microscopic examination of the sediment The urine specific gravity, in pure congestive failure is high in contrast to the figures obtained when the fundamental defect is a *nephropathy* (p 2362)

Microscopic hematuria generally indicates a large renal embolization and infarction suggesting the possibility that a *subacute bacterial endocarditis* (p 1021) has been superimposed

With alleviation of congestive failure there is often a marked *diuresis* amounting to several gallons of urine This happy circumstance often

Treatment

If the management of the patient in shock is to be carried out intelligently the general principles which underlie the preventive and symptomatic treatment require continued consideration Thoughtless therapy may add to the burden and result in a fatality whereas attempts to correct the deranged physiological mechanisms may prove life saving in many instances Shock is a catastrophe of major importance once anoxia has damaged the capillary beds and vital organs the changes are usually irreversible and no known therapy will result in recovery

The aims of the therapist are summarized as follows

1 Removal of shock stimuli
2 Increase of plasma volume
3 Prevention of capillary vasodilatation
4 Prevention of increased capillary permeability
5 Unwillingness to stimulate further vasoconstriction (as by the use of epinephrine) which adds to the capillary disturbance
6 Unwillingness to further diminish cardiac output by the use for example of digitalis unless there are evidences of marked hypotonicity of the myocardium (p 858)
7 Unwillingness to stimulate further the cerebrum and the reception of stimuli by the use of such drugs as caffeine strychnine camphor metrazol and coramine

Prevention of Shock—The prevention of shock is the principal aim of the practitioner who has intimate knowledge of his patient and accompanies him through the travails of shocking experiences such as acute infectious diseases and operative procedures

Psychotherapy—Since each practitioner notes the increased incidence of shock in highly emotional and sensitized individuals it is part of the prophylactic program to reassure the patient and fortify him with full confidence in his eventual recovery The knowledge that the physician is spending the night in the home may contribute more to the prevention of vasomotor collapse in the course of an infectious disease than any other therapeutic agency the presence of the practitioner friend in the anesthesia room and the operating theatre may have more potency than the humble doctor would be willing to admit

Preoperative Care—When an operative procedure is to be one of choice it is wise to have the patient rest in the hospital for several days before the projected procedures A *high protein* diet (p 674) is used *sedatives* are given liberally during the day a *hypnotic* (p 3837) is ordered for night time with a repeat if necessary hypoproteinemia and anemia are corrected by transfusions of whole blood (p 3778)

Basal Anesthesia—Basal anesthesia (p 3912) does much to prevent shock we are advocates of the liberal use of a triple dose of the favorite *hypnotic* 90 to 120 minutes before an anticipated surgical procedure Additionally we favor the injection of the combination of 2 mg of *dilaudid* (1/30 gr) and 0 4 mg of *hyoscine hydrobromide* (1/150 gr) thirty to forty five minutes later We think that the patient with an acute infectious disease is entitled to reasonably liberal dosages of sedatives hypnotics and opiates unless there are cogent reasons that contraindicate them

accompanies digitalization but may also be produced by the mercurial diuretics (p 2261) The diversion of the edema fluid is accompanied by striking loss in weight

Neurologic Symptoms —Few of those who suffer from congestive failure escape without neurologic symptoms Early complaints are often *insomnia* and *terror dreams* probably associated with unrecognized attacks of *paroxysmal nocturnal dyspnea* (p 942) Often the patient fears to go to bed and sits up most of the night adding to the fatigue that is observed during the daytime hours *Cardiac neuroses* (p 897) are of frequent occurrence and usually follow the characterological pattern of the patient in the precongestive phase Often there is profound depression as the sufferer recognizes his limitations referable to work and play

Cardiac Cachexia —Patients with long standing congestive failure become flabby and develop marked *asthenia* and *wasting* often suggesting the syndrome associated with advanced malignancy (p 572) The weight loss may be masked by the accumulated edema Under these circumstances the flabby wrinkled face and arms are in striking contrast to the protuberance of the abdomen and the water logged legs

Peripheral Thromboses —Peripheral thromboses are inevitably encountered in congestive failure most often they are seen in the peripheral veins of the legs especially if there are varicosities Sooner or later they cause *embolizations* which are most often pulmonary

Coronary thrombosis the most ominous of the circulatory complications is elsewhere discussed (p 983)

LABORATORY DATA

Congestive failure is measurable by a variety of laboratory procedures *venous pressure* is elevated (p 788) the *circulation times* are increased (p 787) *blood pressure* readings tend to rise in the early congestive phases and fall progressively as the myocardium weakens the *electrocardiographic tracings* particularly if taken serially provide progressive evidences of coronary insufficiency (p 895) coronary thrombosis (p 983) and myocardial infarction and scarring (p 992) *roentgenograms of the chest* reveal the early evidences of a hydrothorax (p 2032) and disclose the increased lung markings of pulmonary congestion they show also the progressive increase in the cardiac diameter and the changes that accompany the transition from predominant hypertrophy to preponderant dilatation (p 797)

TREATMENT

The treatment of backward failure is aimed at the prevention or elimination of prime causes and efforts directed at symptomatic relief

Prophylaxis

The cardinal fundamental causes for congestive failure are *rheumatic pancarditis* (p 1016) *arteriosclerosis* particularly that involving the coronary arteries (p 976) *essential hypertension* (p 900) *congenital defects* (p 9_3) and *hyperthyroidism* (p 1197) Contrary to the experiences of older clinicians *syphilis* (p 331) is of distinctly minor importance

By the time the patient has reached the stage of backward failure the only fundamental provocative mechanism that is reversible is *hyperthy*

Analgesia—In traumatic procedures immediate and generous doses of analgesics are warranted It is our custom when the patient has severe pain to provide forthright relief by the *slow intravenous injection of an opiate* (p 3853) such as 2 mg of *dilaudid* (1/32 gr) or 16 mg of *morphine sulfate* (1/4 gr)

Heat Versus Cold—There is considerable difference of opinion as to the relative values of heat and cold in the prevention of shock We favor neither of these physical modalties to any degree but try to keep both patient and room temperature at some comfortable medium We are as much opposed to excessive bundling with blankets hot water bottles and electric pads as we are to applications of ice

Anesthetic—The choice of anesthetic is important in the patient who is a candidate for shock We favor the use of basal anesthesia as previously described (p 3912) and we prefer inhalation gas to local or spinal anesthesia If the last is to be employed an attempt is made to sustain the level of blood pressure by the oral or subcutaneous administration of ephedrine 1 per cent neosynephrin or paredrine

The Treatment of Impending Shock—The treatment of impending shock includes the continuance or the resumption of the measures used in the prophylactic program

Adrenergens—In this phase when there is not yet any intense vasoconstriction the controlled use of the *adrenergic drugs* has considerable value *epinephrine* in oil may be given using 0 3 cc as the initial dose *ephedrine sulfate* may be given orally in capsules containing 0 025 gm (3/8 gr) *neosynephrin* in 1 per cent solution may be injected subcutaneously Every effort is made to prevent the injudicious production of such marked vasoconstriction as to elevate blood pressure beyond the capacity of the heart to make an adequate response The practitioner remembers that the use of the vasoconstrictors is not an unmitigated blessing If these preparations seem helpful they are to be continued if as particularly happens following the injections of posterior pituitary extract the patient appears to be more shocked their use is contraindicated

Sedatives—Pain and restlessness are allayed with *opiates sedatives* and *hypnotics* In an operative procedure the technical manipulations are interrupted in the case of injury a policy of skilful neglect is inaugurated

Gravity and Warmth—An attempt is made to correct cerebral ischemia by raising the legs and body of the patient so that blood tends to gravitate into the cranium body temperature is maintained by the use of blankets excessive heating with electric pads hot water bags and multiple coverings is avoided

Compression Bandages—Snug compression bandages are applied to three of the four extremities leaving one arm free for blood pressure readings and the necessary intravenous injections

Intravenous Infusions—Impending shock requires that efforts be made to increase plasma volume this may be accomplished by intravenous infusions of plasma (p 3778) or whole blood The intravenous drip is started with saline or dextrose in saline until plasma or blood can be obtained in shock accompanying hemorrhage whole blood is the indicated infusate

Sodium Lactate—A revolutionary principle of therapy that promises to obviate the necessity for intravenous infusion is the oral administration

roidism The relief of this metabolic derangement by preliminary iodization and later *subtotal enucleation of the gland* (p 1215) occasionally results in a phenomenal restitution to an *approximate norm*

Alterations in the 'Way of Life —The patient with congestive failure is often in the position of an individual whose income has been sharply curtailed *Luxuries must be abandoned* the scale of living must be pared down cakes and ale become memories while the daily subsistence emphasizes bread and milk'

In the presence of congestive heart failure it is the function of the *practitioner to sit down* with the patient and his family and discuss ways and means Those who must continue to earn their living are required to renounce all extraneous activities they are to return home immediately at the end of the working day and retire to bed until it is time to arise *for resumption* of the activities of the succeeding day and at the end of the working week a *rest cure* is attempted in the home Stairs are avoided heavy work is delegated to other members of the household or co workers *domestic* scenes and the tensions of everyday living are reduced to a *minimum* The intake of alcohol is reduced to a single drink taken at the *end of the* working day smoking is limited to an occasional cigarette after working hours excesses of any type are avoided and moderation is urged *in all things*

Those who can afford to are urged to retire they are stimulated to become interested in some hobby or avocation (p 3760) so as to avoid the depression that is associated with a useless existence It should be the function of the physician to stress purposeful living rather than a prolongation of the act of dying

Restriction of Physical Activity —The cardiac invalid is urged to engage in as much physical activity as is compatible with comfort Soft and flabby muscles are no help to a failing circulation It is even more important for the cardiac to keep in trim than his less handicapped fellow Exercise is best accomplished by gentle walking simple calisthenics (p 3756) the less strenuous household chores gardening boating lawn games a few holes of golf over a relatively flat course and indoor games

Psychotherapy —The practitioner fulfils no more useful purpose than that of acting as psychotherapist to his patient who is compelled to accept the restrictions of life demanded by his reduction in cardiac capacity After emphasis upon necessary limitations the physician friend must stress the amenities of the more sedentary manner of living The patient is urged to take up with hobbies and avocations religion often offers its solace reading listening to music and the better radio programs fill the day Often the local cleric may be enlisted by the practitioner in his attempt to salvage the patient from boredom, allay his restlessness and prevent the development of the depression that occurs in those who spend their days waiting for the inevitable visit of the grim reaper

The Rest Cure —The rest cure is of inestimable value in the prophylaxis of backward failure A Weir Mitchell routine (p 3754) will save many a congestive episode by the simple expedient of going to bed for a period of a week or a month, the compromise of a week end in bed or a cure day' once a week may be equally successful in those who must continue their labors Bed rest is mandatory if the patient acquires an incidental

of sodium lactate To prepare the isotonic (one-sixth molar) 1 75 per cent solution of sodium lactate 72 gm of syrup of sodium lactate are put into a liter bottle which is then made up to volume with cold tap water The solution must be made up fresh as it tends to become sour

The patient is required to drink 7 to 10 liters of lactate within the first twenty four hours if there is vomiting or lack of cooperation a continuous drip is administered by way of a Levine tube passed through the nose (p 1750)

After the first day sufficient fluid is administered so that the daily urinary output approximates 1500 or 2000 cc As soon as food is tolerated a high protein diet (p 674) is given supplemented by the administration of 50 to 100 gm of *amino acids* by intravenous drip if necessary

Oxygen—There can be little doubt as to the advisability of combating tissue anoxia by the inhalation of high concentrations of oxygen If respirations are shallow or depressed 5 to 10 per cent carbon dioxide is supplied with the oxygen

Summary—A summary of the measures to be used in the treatment of impending shock in the order in which they should be employed is under noted

1 Reassurance
2 Cessation of operative procedure
3 Avoidance of causing further trauma by transportation or attempts to reduce fractures or cleanse wounds
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5 Elevation of the foot of the bed
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8 Sedation
9 Analgesia
10 Bandaging of extremities
11 Inhalations of oxygen
12 Ingestion of sodium lactate
13 Intravenous infusion of plasma
14 Transfusion of whole blood with hypoproteinemia or hemorrhage
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16 Continued vigilance with shifting of orders where necessary
17 Avoidance of vasoconstrictors in more profound degrees of shock avoidance of the use of digitalis caffeine strychnine camphor coramine metrazol or any other preparation that will tend to diminish venous inflow or cardiac output or which will make the patient more alert to the reception of sensory stimuli Colloidal solutions such as acacia pectin and isinglass are not recommended since they are difficult to obtain and are not so inert as plasma
18 Rapid hemostasis and the restoration of the lost blood through the use of a blood transfusion

Treatment of Fully Developed Shock—With the exception of the use of adrenergic drugs fully developed shock is treated in the manner of the

respiratory infection or if there is any evidence of strain and tension in the household

Weight Reduction.—A considerable burden of cardiac work may be relieved by judicious weight reduction wholly aside from the factor of the elimination of edema fluid The use of an *abdominal binder* or corset is helpful in obese emphysematous cardiacs

Dietotherapy.—The low calory diet is distinctly in order for those who are overweight (p 669) The loss of excess fat and a diminution in the size of a redundant panniculus constitute remarkably effective measures in reducing the work of the heart and relieving symptoms particularly breathlessness

Prevention of Infection.—An attack of backward failure is often precipitated by some intercurrent invasion such as the simple upper respiratory infection the nasal occlusion the constant cough and the sleepless nights seem sufficient to make the difference between cardiac compensation and backward failure For this reason the patient is urged to take every precaution to avoid catching cold

Younger cardiacs whose *affliction is on the basis of a rheumatic fever* are prevented from developing exacerbations by the continued administration of *sulfonamide* in daily doses of 1 to 1.5 gm (15 to 22½ grains)

Surgery.—*Subtotal thyroidectomy* is mandatory in those with manifestations of masked or occult hyperthyroidism (p 1205) *Ligation of a ductus arteriosus* (p 957) is a life saving measure in those who are afflicted with this congenital abnormality The various operative procedures involving the adrenergic fibers of the involuntary nervous system provide less spectacular protection in patients with *essential hypertension* (p 900)

Climatotherapy.—The case for climatotherapy is elsewhere debated (p 3761) The affluent may be somewhat benefited by a more equable climate children with rheumatic fever seem to have fewer attacks while living in semi tropical regions In general however the boons of climatic transplantation are far outweighed by the economic sacrifices required and the necessity of transplanting the home or separating from the family circle

Spa Therapy.—*Spa therapy (p 3764) is only for the affluent* Actually no more benefit is accomplished at the cure place than can be obtained by a competent physician taking care of his patient in a well-equipped home The spa does however furnish a reason for escape (p 3754) *fractious individuals often follow a routine which they will not obey* within the confines of their own dwelling place If the expense of travel to the spa and maintenance are not a drain on the individual or his family group *cure therapy may be highly advisable*

Often the spa accomplishes the purpose of teaching the patient his routine there he becomes used to the low calory diet with diminution in the amount of alcohol caffeine and tobacco He is divorced painlessly from the routine of his daily chores the woman gets away from her household long enough to have other members of the family take over her domestic duties and the interlude provides a therapeutic transition period for the adjustments necessary both to the patient and to the immediate family group

Contraception.—The female cardiac of child bearing age should enter a complete discussion of the hazards of pregnancy long before this possibil

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ity is an actuality Many factors other than medical enter the consideration There are religious scruples against the practice of contraceptive devices many women have a maternal urge that is so strong that it is as futile to argue against it as against the elements

In general it is inadvisable for any woman to contemplate pregnancy if she has had any of the clinical manifestations of backward failure However if she is hellbent to bear a child she may be encouraged by the knowledge that the circulatory system usually responds beyond all expectation to the excessive demands of gestation and parturition

Symptomatic Therapy

The symptomatic therapy of backward failure involves efforts to diminish cardiac work procedures to aid in the elimination of edema fluid and measures designed to increase cardiac efficiency

Procedures Designed to Diminish the Work of the Heart.—Those procedures designed to diminish the work of the heart have been summarized in the section on prophylaxis (p 945) The patient is put to bed if it is at all possible those who suffer from dyspnea and orthopnea should purchase a *hospital bed* so that they may sleep in an optimum position of semirecumbency The importance of frequent change of position is urged and an inflated rubber ring is placed under the buttocks and pressure points to avoid the development of bed sores

The cardiac invalid is often restless and fussy while in bed Under these circumstances it is wise to inaugurate a daily routine employing the devices of reading directed radio listening scheduled visits and occupational therapy (p 3760)

Sedation—Relaxation is furthered by the administration of a *sedative* after meals and for this purpose *phenobarbital* in doses of 16 mg (¼ gr) is preferred A hypnotic such as *sodium seconal* (p 3841) is advisable at bedtime with a repeat order if the need arises

Dietotherapy—Diminution in physical activity calls for a corresponding diminution in food intake The optimum routine plans for *several meals* whose total *caloric value* no more than meets basic needs the average individual is best given 1000 to 1200 calories for a twenty four hour stoking (p 669) *fluid intake* is kept at such a level that a urinary output *of 1000 to 1500 cc is maintained salt* may be used in the preparation of food but should not be used at the table

With failure of simple dietotherapy in the control of edema more stringent measures require consideration Older clinicians favored the low calory restricted fluid regime of Karell (p 670) but modern investigations advocate unlimited fluids and a restricted sodium intake as outlined on p 682

Oxygen Inhalation—Inhalations of oxygen are not reserved for those patients who are in urgent distress Early self treatment with oxygen serves the useful psychotherapeutic purpose of taking the ominous implication from the presence of the oxygen tank The use of the newer devices modelled upon apparatus employed by aviators may be taught the patient

A few minutes of copious oxygenation every few hours accomplishes a great deal in the prophylaxis of backward failure it relieves breathlessness and anginal pain better than most drugs and it may be rapidly employed without any fear of serious aftermath The cost after the initial

of sodium lactate To prepare the isotonic (one-sixth molar) 1 75 per cent solution of sodium lactate 72 gm of syrup of sodium lactate are put into a liter bottle which is then *made up to volume with cold tap water* The solution must be made up fresh as it tends to become sour

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Treatment of Fully Developed Shock—With the exception of the use of adrenergic drugs fully developed shock is treated in the manner of the

expenditure is relatively negligible the presence of the machine promising rapid and early relief of distress gives the patient a feeling of great security

Procedures Used to Aid in the Elimination of Edema Fluid—The cardinal symptoms of congestive failure are due to the accumulation of fluid in the tissue spaces In *left ventricular failure* it is the lungs that become congested in *right ventricular failure* the tissues of the systemic vascular surface become waterlogged The removal of fluid constitutes an important part of the routine in the treatment of cardiac failure

Restriction of Fluid and Salt—Except to a limited degree we are not strong advocates of rigid restrictions of the intake of fluid and salt While we forbid the use of *salting* at table we do not believe that there is sufficient to be gained by avoidance of salt in cooking to justify the consequent monotony of the diet except in extreme instances (p 682)

We do not favor rigid restriction in *fluid intake* a daily limitation of fluid to less than one liter works great hardship adding a great deal more to the cardiac burden than less rigid adherence to accepted routine We make an effort to have the patient take as little fluid additional to his meals as is compatible with comfort Some patients rarely drink the equivalent of a liter of fluid others are miserable if they cannot have up to 1500 cc We obey no rules of thumb relative to the problem the general principle is explained to the patient who is asked to keep track of daily fluid intake and output With continued edema the physician may try either the low calory restricted fluid regime of Karell (p 670) or the low sodium diet (p 682) with unrestricted fluids

The Diuretics—The pharmacology of the diuretics is elsewhere discussed in detail With rare exception our preference is for the use of ammonium chloride and the mercurials See p 2257

Ammonium chloride is prescribed in enteric coated tablets each containing 0.5 gm (7½ grains) Of these eight to twelve are given daily for at least three days with an intermission of one or two days depending upon the changes in body weight The acidifying salts may be actively diuretic they prevent the reaccumulation of fluid and they act synergistically with the mercurials next to be described

The reintroduction of *mercurial diuresis* in the program for the management of the cardiac invalid constitutes one of the most important therapeutic accomplishments of recent times The best guide for the use of the preparation is an accurate observation of body weight a gain in weight is noted considerably before visible edema is observed in the subcutaneous tissues or the serous cavities The mercurial may be given alone but it is frequently more efficient if given after a forty eight hour ingestion of the acidifying salts such as ammonium chloride The intravenous injection of bile salts to supplement the mercurial effect has no advantage over the simpler oral use of the salts

We favor the *intramuscular injection* of 1 or 2 cc of any one of the popular organic mercurials provided in ampoule form by the manufacturers In a dire emergency such as an acute pulmonary edema it may be necessary to give the drug *intravenously* but serious discomfort may accompany this route of administration and an occasional death has been observed

The mercurial diuretics are available also for *oral administration* It is

impending syndrome except that efforts are required to be more vigorous and more sustained

The contraindication to the continued use of adrenergic drugs is based on the compensatory vasoconstriction that accompanies capillary dilatation and serves further to decrease the venous return to the heart Furtherance of this ill conceived response adds to the physiological derangement despite the best of intentions

There is a great tendency to throw discretion to the winds in increasing shock and attempt to blitz the patient into recovery The practitioner must make every effort despite the overwhelming weight of pressure to avoid this error He may rest assured that no good and only harm can follow the uses of caffeine camphor, metrazol coramine strychnine and the like

The course of events is best followed by blood pressure readings and hematocrit determinations favorable progress is suggested by resumption of a normal systolic level and lessened hemoconcentration evil signs include progressive fall of systolic tension and increased hemoconcentration

our opinion that this method which corresponds to the use of the Guy s Hospital Pill of the eighteenth century is less desirable than intramuscular injection its use should be reserved for patients who live at a great distance and who cannot have a bi weekly visit from the physician The oral dose of the mercurial diuretic consists of 3 to 5 tablets of Salyrgan Theophylline given shortly after breakfast The product is enteric coated and contains 80 mg (1¼ gr) of Salyrgan and 40 mg (⅔ gr) of the xanthine

In the presence of marked renal impairment mercurial diuretics must be used with some caution However the mere presence of albuminuria should not deter the physician from employing these useful preparations there is no clinical evidence to show that the heavy metal produces any significant or permanent renal damage

The diuretics other than ammonium chloride and the mercurials seem curiously ineffectual in comparison with these potent preparations The various *xanthines* (p 2261) such as *theophylline* (theocin) *theobromine theocalcin diuretin* and *aminophylline* have widespread promotion but our experiences leave us with considerably less than an enthusiastic respect for their diuretic properties

Urea (p 2260), in doses of 50 to 100 gm daily often provides effectual diuresis but its evil taste more than offsets its therapeutic action

Mechanical Measures—Once a hydrothorax or an ascites has developed there is slim likelihood that the fluid may be withdrawn from the serous cavity by diuretics (p 2257) Sooner or later a *thoracentesis* (p 2030) or an *abdominal paracentesis* (p 1920) becomes indicated These procedures are often followed by a tremendous improvement in cardiac efficiency and their performance should not be too long delayed Attention is drawn to the possibility that either of these measures may be associated with *vasovagal syncope* (p 921) to prevent this complication the patient is prepared by a preliminary dose of a sedative or an opiate and local anesthesia is used

Procedures Aimed at the Increase of Cardiac Efficiency—Cardiac efficiency is directly improved by lessening the blood volume and by the indicated use of digitalis and quinidine

Phlebotomy—Phlebotomy is a useful and somewhat neglected form of therapy It is indicated particularly where there is pulmonary edema or hepatic venous engorgement The individual of average size may profit considerably by the removal of 500 cc of blood obese and plethoric patients may stand well the removal of 800 to 1000 cc By diminishing the venous return to the right heart phlebotomy permits the organ to correct the discrepancy that exists between venous return and ventricular output

The bloodless phlebotomy is accomplished by application of tourniquets or blood pressure cuffs to the extremities so as to obstruct venous return but not impede arterial inflow The blood temporarily pools in the limbs pressure is applied to two extremities at a time with alternation every twenty minutes

Quinidine—The indications for the use of quinidine are elsewhere delineated (p 861) The drug is of value in restoring normal sinus rhythm in the presence of cardiac arrhythmias (p 873) such as the premature

CHAPTER 42

PHYSIOLOGICAL DISTURBANCES OF THE CIRCULATORY SYSTEM CIRCULATORY DEFICIENCY BACKWARD FAILURE

BACKWARD FAILURE (CONGESTIVE FAILURE CHRONIC PASSIVE CONGESTION)

Backward failure of the circulatory mechanism may be of *central* or *peripheral* origin In the first instance the cardiac pump is unable to eject at each ventricular systole an amount of blood equal to that returned in the diastolic filling period when the disturbance is essentially peripheral the resistance in the blood bed rises to the point where the pumping mechanism is overwhelmed and there is backing up in the distensible venous system

Pathologic Physiology —Backward failure eventually involves both chambers of the heart In some instances however the primary breakdown may be predominantly left or right sided

Left Heart Failure —Left heart failure is the more common variety It is usually the result of *hypertension* (p 900) *aortic stenosis* or *insufficiency* (p 970) or *coarctation* or *stenosis* of the *aorta* (p 959)

In the early asymptomatic phase of the disturbance the ventricle undergoes *hypertrophy* as elsewhere described (p 869) Later when it *dilates* (p 772) the contractile power is lessened the left auricle fails and blood is pooled in the distensible pulmonary veins and capillaries the inefficient oxygenation of the blood leads to further embarrassment of the hypertrophied heart muscle and sooner or later the strain is transferred to the right circuit which also evinces the evidences of functional impairment (p 787)

The *clinical manifestations* of left heart failure are essentially respiratory The patient notes that his wind is failing' and becomes *breathless* as the result of any unusual effort Once the breath is lost it takes an unaccustomed span of time for recovery The sufferer is compelled to sit down and "rest a bit and when activity i resumed it is not with accustomed vigor and elasticity an extra pillow is required at night and then another until the mo t comfortable position for sleep is semi recumbent Members of the family and co-workers note that the now potentially cardiac invalid pants a bit even at rest and that the chest heaves more than has been its custom One night there is an attack of *paroxysmal*

contraction (p 877) auricular fibrillation (p 885) and auricular flutter (p 883)

Digitalis—The potentialities of digitalization require a complete understanding of the physiology of the circulation (p 771) and the pharmacology of the drug (p 854) In general the prime usefulness of digitalis is in backward failure due to *permanent auricular fibrillation* (p 858) Under this circumstance a partial heart block is established so that the ventricular rate is slowed and cardiac efficiency is improved Less often *digitalis is helpful in the restoration of sinus rhythm* when paroxysmal irregularities such as auricular flutter (p 883) paroxysmal tachycardia (p 873) and auricular fibrillation (p 885) are encountered

The use of digitalis in backward failure associated with *sinus rhythm* is dependent upon its efficacy in restoring normal tonus to a dilated myocardium in our experience each therapeutic test constitutes an experiment in which the patient may be benefited harmed or unaffected depending upon individual circumstances (p 854)

PREPARATIONS AND DOSES—We favor the use of the standardized *powdered leaf of digitalis purpurea* for routine use The preparation is most

TABLE 8—DOSAGE OF DIGITALIS IN BACKWARD FAILURE

	Tablets	Grains
Immediate dose	6–8	9–12
4–6 hours later	3–4	4½–6
6 hours later	3–2	4½–3
6 hours later	3–1	4½–1½

conveniently prescribed in *compressed tablets* each containing 0 1 gm (1½ grains)

The effective digitalizing dose for the adult of average size approximates 15 tablets (22½ grains) in the first 24 hours In an emergency 6 to 8 tablets may be given as the initial dose (9 to 12 grains) half this amount is ordered in 4 to 6 hours (4½ to 6 grains) the remainder of the daily quota is given in equal doses after 12 to 18 hours

If for any reason the powdered leaf is not available or proves unsatisfactory the preparation of our choice is *digoxin* a product of *digitalis lanata* This drug is marketed in tablets containing 0 00025 gm (1/40 grain) A full digitalizing dose for the adult of average size approximates 6 tablets (0 0015 gm) These are given immediately if the need is great and no digitalis preparation has been given in the recent days A single tablet is given thereafter every four hours until a full effect is noted or evidences of toxemia appear

In a dire emergency digoxin is injected *intravenously* For direct injection the product is ampouled in 1 cc vials containing 0.5 mg (1/120 grain) *This solution is diluted to 10 cc* with saline cloudiness may be disregarded The *injection must be slow* infiltration causes extreme irritation The effect of the drug is noted in 5 to 10 minutes and a maximum

nocturnal dyspnea with its terrors', the ominous *bubblings* of the frankly audible edematous rales are heard, and spells of *coughing* are induced by the exudation of fluid into the pulmonary alveoli

Physical and laboratory examinations reveal evidences of dilatation and failure of the left circuit (p 870)

Right Heart Failure—Right heart failure is usually due to the presence of a *mitral stenosis* (p 970), *emphysema* (p 2056) *pulmonary fibrosis* (p 2199), extensive *bronchiectasis* (p 2059) *sclerosis* of the *pulmonary arteries* (p 994) *left heart failure*, or the congenital syndromes of *pulmonary stenosis* (p 961) the *tetralogy of Fallot* or the *Eisenmenger complex* (p 961) The signs of right heart *hypertrophy* (p 867) and *dilatation* are observed (p 870) the neck veins become engorged, the liver is enlarged and tender, *edema* is noted in the dependent parts fluid accumulates within the thorax and the peritoneal cavity

The *clinical manifestations* of predominantly right heart failure are often insidious They may be deceptively referable to the *digestive system* with loss of appetite nausea and pain or discomfort in the epigastric region or the right hypochondrium, *pretibial edema* is noted at the end of the day removal of the shoes leaves pressure marks the phenomenon of *pitting* is clearly discerned *weight* increases despite a diminished intake of food and some loss of strength and endurance

The phenomena of congestion are observed in the systemic venous channels the waist of the heart fills out *neck veins* become engorged the *liver* enlarges and is tender fluid is noted within the thoracic and peritoneal cavities pressure on the distended liver increases the distention of the neck veins (*hepatojugular reflux*)

CLINICAL MANIFESTATIONS

The clinical manifestations of backward failure are varied and involve all body organs and systems

Dyspnea —The symptom of *breathlessness* (p 2016) is essentially due to left heart failure It passes through the progressive phases of exertional dyspnea, dyspnea at rest particularly during the evening orthopnea paroxysms of nocturnal dyspnea, so called cardiac asthma and the terminal respiratory irregularities due to involvement of the vasomotor center as in Cheyne-Stokes respiration

Cyanosis —With increasing concentrations of reduced hemoglobin in the peripheral vascular tree the onset of cyanosis is observed Partially this phenomenon results from imperfect exchange of gases in the congested lungs, it is also favored by prolonged stasis of the circulating fluid in the tissues

Edema —Cardiac edema results primarily from increased venous pressure due to right heart failure (p 942) Subsidiary factors include increased pressure within the thoracic duct impairment of lymphatic drainage, hypoproteinemia (p 706), diminished tissue elasticity diminished blood supply to the involved areas and peripheral anoxia Each successive step adds to the burden imposed by those which have come before finally there is anoxia of the myocardium coronary insufficiency and congestion of the vasomotor center are encountered until the compensatory mechanisms are no longer capable of coping with the ever mounting demands

our opinion that this method which corresponds to the use of the Guy's Hospital Pill of the eighteenth century is less desirable than intramuscular injection its use should be reserved for patients who live at a great distance and who cannot have a bi weekly visit from the physician The oral dose of the mercurial diuretic consists of 3 to 5 tablets of Salyrgan Theophylline given shortly after breakfast The product is enteric coated and contains 60 mg (1¼ gr) of Salyrgan and 40 mg (⅔ gr) of the xanthine

In the presence of marked renal impairment *mercurial diuretics must* be used with some caution However the mere presence of albuminuria *should not deter* the physician from employing these useful preparations there is no clinical evidence to show that the heavy metal produces any significant or permanent renal damage

The diuretics other than ammonium chloride and the mercurials seem curiously ineffectual in comparison with these potent preparations The various *xanthines* (p 2261) such as *theophylline* (theocin) *theobromine theocalcin diuretin* and *aminophylline* have widespread promotion but our experiences leave us with considerably less than an enthusiastic respect for their diuretic properties

Urea (p 2260), in doses of 50 to 100 gm daily often provides effectual diuresis but its evil taste more than offsets its therapeutic action

Mechanical Measures—Once a hydrothorax or an ascites has developed there is slim likelihood that the fluid may be withdrawn from the serous cavity by diuretics (p 2257) Sooner or later a *thoracentesis* (p 2030) or an *abdominal paracentesis* (p 1920) becomes indicated These procedures are often followed by a tremendous improvement in cardiac efficiency and their performance should not be too long delayed Attention is drawn to the possibility that either of these measures may be associated with *vasovagal syncope* (p 921) to prevent this complication the patient is prepared by a preliminary dose of a sedative or an opiate and local anesthesia is used

Procedures Aimed at the Increase of Cardiac Efficiency—Cardiac efficiency is directly improved by lessening the blood volume and by the indicated use of digitalis and quinidine

Phlebotomy—Phlebotomy is a useful and somewhat neglected form of therapy It is indicated particularly where there is *pulmonary edema or hepatic venous engorgement* The individual of average size may profit considerably by the removal of 500 cc of blood obese and plethoric patients may stand well the removal of 800 to 1000 cc By diminishing the venous return to the right heart phlebotomy permits the organ to correct the discrepancy that exists between venous return and ventricular output

The bloodless phlebotomy is accomplished by application of tourniquets or blood pressure cuffs to the extremities so as to obstruct venous return but not impede arterial inflow The blood temporarily pools in the limbs pressure is applied to two extremities at a time with alternation every twenty minutes

Quinidine—The indications for the use of quinidine are elsewhere delineated (p 861) The drug is of value in restoring normal *sinus rhythm* in the presence of cardiac arrhythmias (p 873) such as the premature

Fever—An aseptic pyrexia usually accompanies backward failure In all likelihood this results from *pulmonary hypostasis* which is inevitably followed by an insidious low grade *pneumonitis* (p 2185) The latter is often associated with a moderate *leukocytosis*

Elevation of the Basal Metabolic Rate—In congestive heart failure the basal metabolic rate is usually elevated due to increased oxygen consumption by *the heart and the heightened respiratory efforts* that are associated with the dyspnea It is of great importance to differentiate the elevated basal metabolic rate of congestive failure from that due to a more fundamental *hyperthyroidism* (p 1197) In the latter instance the *therapeutic test with iodide* (p 1213) is often conclusive relief of the circulatory phenomena by the drug suggests the consideration of a *subtotal thyroidectomy* (p 1215)

Gain of Body Weight—The practitioner gains invaluable information concerning the course of congestive failure by the simple observation of body weight Increases point to the accumulation of edema fluid and the advance of the congestive failure loss of weight accompanied by diuresis is a favorable prognostic sign attesting to the recuperative powers of the organism and the happy choice of the therapeutic procedures

Daily observations of the fasting stripped weight are the most valuable indices of the course of events they provide signposts for the prescription of the mercurial diuretics (p 2261)

Circulatory Symptoms—The heart makes a variety of efforts to sustain the *increasing burden the muscle fibers hypertrophy the cavities dilate* and the minute rate rises When the burden becomes too heavy untoward cardiac phenomena are observed The rhythm becomes irregular the variety of the *arrhythmias* progressing from simple premature contractions to paroxysms and then permanent episodes of auricular fibrillation With myocardial ischemia *precordial oppression is noted Attacks of angina pectoris* (p 890) are reported There are ominous episodes of *acute coronary closure* with varying degrees of *myocardial infarction* (p 992) inevitably the patient progresses to permanent *cardiac invalidism*

In the early stages of circulatory failure the *blood pressure* rises as the result of asphyxia of the vasomotor center later there is a progressive fall particularly noted in those with an initial hypertension

Respiratory Symptoms—*Cough* is an early and persistent symptom of the pulmonary *congestion of left heart failure* In the phase of engorgement it is nonproductive It is particularly harassing in the attacks of paroxysmal nocturnal dyspnea Later when there is *pulmonary edema* the cough is accompanied by pink foamy sputum In *chronic pulmonary congestion* as seen in mitral disease the sputum appears rusty and contains heart failure cells laden with *hemosiderin* (p 3720) *Pulmonary infarction* is often first manifest by the appearance of bright red globules of sputum or by a frank *hemoptysis* (p 2058) When there is a secondarily imposed *hypostatic pneumonitis* the sputum becomes purulent and *tenacious*

Hypostatic Pneumonitis—See p 2193

Hydrothorax—The accumulation of fluid in the pleural cavity produces the physical signs of a hydrothorax There is increasing *dulness* to *flatness* the *breath sounds* are diminished and then absent *fremitus* can no longer

CHAPTER 43

ORGANIC DISEASES OF THE CIRCULATORY SYSTEM
INTRODUCTION CONGENITAL ABNORMALITIES

MANY of the physiological derangements of the circulatory system occur in morphologically damaged structures The sections which follow deal with organic diseases of the heart arteries veins and lymphatics

Classification —The morphological derangements of the circulatory system are presented in the following main categories

Circulatory Phenomena Associated with Systemic Derangements Congenital Abnormalities Neoplasms (p 967) Mechanical Disturbances (p 967) Arteriosclerosis (p 976) Neurogenic Afflictions (p 1000) Inflammations and Infections (p 1005)

CIRCULATORY PHENOMENA ASSOCIATED WITH SYSTEMIC DERANGEMENTS

There is no bodily disturbance which is not accompanied by some functional alteration in the circulation In Table 59 are tabulated the more commonly encountered lesions of the heart and its vascular channels which are the result of specific systemic disorders

CONGENITAL CARDIOVASCULAR DISEASE

Congenital heart disease accounts for two per cent of organic cardiac lesions In the past all too frequently the diagnosis of congenital heart disease was made at autopsy the ingenious uses of fluoroscopy teleo roentgenology and angiocardiography have clarified many previously obscure lesions

Accuracy of diagnosis in congenital cardiac disease is not a mere academic exercise since it is an important basis for prognostication and treatment The outlook for many minor defects is good but the unusual susceptibility of the congenital cardiac to rheumatic fever (p 1010) and subacute bacterial endocarditis (p 1021) makes accurate diagnosis an important aid in the conduct of the prophylactic and remedial aspects of antibiotic therapy and in establishing indications for surgery (p 965)

ETIOLOGY

The causes for the development of congenital cardiovascular disease are unknown When the complicated mechanism required to construct the

be prevented by proper ventilation and cooling of the sickroom If present they may be relieved by hydrotherapy and the sparing use of antipyretics sedatives or hypnotics (p 383)

MAINTENANCE OF MORALE

Quite as important as the care of the body is the maintenance of morale particularly in prolonged diseases The atmosphere of the sick room must be as cheerful as is compatible with the prognosis An occasional visitor who comes for a stated limit of time and who has the good sense to discuss only the nonmedical topics of the day is often very welcome The presence of more than a single visitor gives rise to cross conversation and confusion Prolonged visits are a greater strain on the patient than on the visitor Friends are often more welcome than relatives and the physician must diplomatically encourage the one and discourage the other

The use of the radio or phonograph the reading of the newspapers or light fiction and simple games such as jigsaw puzzles tend to maintain the cheerful attitude of the sickroom

SURGERY IN INFECTIOUS STATES

Many of the infectious diseases have surgical implications Suppuration *occurs in staphylococcic and streptococcic invasions otitis media is com*monly encountered in the upper respiratory infections and certain of the exanthems empyema complicates lobar pneumonia liver abscesses result from amebiasis and peritonitis is met with in a large variety of enteric disorders

The miracles of anti infective therapy have greatly reduced surgical complications in the infectious diseases Nevertheless the practitioner must be on the alert for their recognition and must give the specialist or the general surgeon an early opportunity to see the patient Only in this way is the patient given the advantage of a judgment based on continued observation rather than a single kaleidoscopic glance

SPECIFIC ANTI INFECTIVE THERAPY

The prevention and treatment of the infectious diseases are accomplished by specific immunotherapeutic chemotherapeutic and antibiotic agencies These powerful modalities are utilized by the practitioner in the concerted manner in which the modern general combines the military forces of land air and sea

In an attempt to integrate the vast material of specific anti infective therapy the remainder of this chapter is devoted to a discussion of (1) immunity and (2) the specific anti infective agents The individual management of each infection is elsewhere considered in separate chapters

NATURAL AND ACQUIRED IMMUNITY

Resistance to infection is a function of the cells and humoral agencies The cells provide a mechanical barrier and are capable of destroying invaders chiefly by *phagocytosis* Cells and circulating fluids elaborate *antibodies* for direct attack upon micro organisms and neutralization of toxic products

The Mechanical Defenses—The unbroken skin and mucous membranes

or semi fluid The patient should not be asked to take foods that are bulky or that require mastication No nutritive value is lost in the soft diet (p 668)

The most important desideratum in the dietary intake is the maintenance of the protein metabolism The patient of average size should receive at least 100 gm of protein yielding 400 calories and mostly provided in milk and the dairy products particularly cheese ice cream and custards The remaining protein requirements may be met by finely divided meat fish or poultry served as the hamburger scraped beef creamed chicken or a fish souffle Contrary to general belief meats do not elevate the temperature If distention results from the milk ingestion the other food stuffs are substituted

The remaining caloric needs are made up mostly by starches and carbohydrates very little fat being employed in order to avoid acidosis The carbohydrates and starches may be provided by fruit and fruit juices cold and hot cereals with added sugar bread and crackers with jam marmalade or honey candy syrups custards or puddings soda water or the popular carbonated drinks potato spaghetti macaroni or noodles

In the longer fevers accessory vitamins are administered in convenient form (p 616)

CARE OF THE BOWELS

The care of the bowels in the febrile is best accomplished by a simple daily enema Previously it was the custom to purge thoroughly at the initiation of the febrile illness This practice is still in vogue in the treatment of the upper respiratory infection and is conducive of nothing but harm Fluids are lost the frequent necessity for evacuation fatigues the patient griping may occur irritation of enteric lesions such as the Peyer s patches in typhoid fever may lead to continuation of the diarrhea or even the more serious complications of hemorrhage and perforation Actually nothing noxious is removed referable to the specific invader or its toxins

To prevent fecal impaction a dose of mineral oil is given at bed time A glycerine suppository may be inserted in the morning Failing a result a small glycerine or soapsuds enema to wash out the bowel should suffice Irrigations and so called high enemas accomplish little more than the cleansing enema They are practiced only through ignorance

TREATMENT OF ILEUS

Most febrile illnesses are complicated sooner or later by ileus or distention Mostly this is due to dietary error particularly the employment of excessive amounts of milk or the over liberal use of fruit juices and carbonated drinks It is not at all unlikely that iced drinks produce distention irrespective of their chemical composition

The prevention and treatment of ileus are concerned with reducing the amount of milk stopping the fruit drinks and the carbonated beverages and serving warm drinks and foods These dietary proscriptions plus a cleansing enema will take care of most instances of ileus The remainder may be most easily relieved by the use of stimulants of the intestinal musculature notably neostigmine (p 1851)

TREATMENT OF NERVOUS SYMPTOMS

Very few prolonged febrile illnesses run their course without the complaint of restlessness headache or insomnia For the most part these can

ventricular slowing is observed in 1 to 2 hours The dose may be repeated if necessary at the end of the second hour

RESULTS —The best digitalis results are obtained in *auricular fibrillation* with a pulse deficit The ventricular rate slows the deficit disappears edema lessens with effectual diuresis and symptoms abate An attempt is made to hold the ventricular rate at 70 to 80 with daily maintenance doses of 1½ grains of the powdered leaf or 1/120 grain (0 0005 gm) of digoxin

In backward failure with *sinus rhythm* the effects are less spectacular and poisoning may be encountered Only careful clinical observation in the individual patient, determines the advantages or disadvantages of digitalization

In the event of failure no better effects may be anticipated from shifting to allied preparations such as strophanthus ouabain squill or digitalis proprietaries

Surgery —Surgical attempts to diminish the cardiac burden have been offered in the procedures of *pericardiectomy* and *total thyroidectomy*

The skilled and experienced specialist surgeon may lessen the cardiac burden dramatically by pericardiectomy in *chronic pericarditis* (p 1011) total thyroidectomy in chronic backward failure ligation of the patent ductus arteriosus (p 959) reconstruction of a coarcted aorta (p 960) the creation of arterial shunts in certain congenital cyanotic lesions (p 962) and ligation of arterio venous fistulas or aneurisms

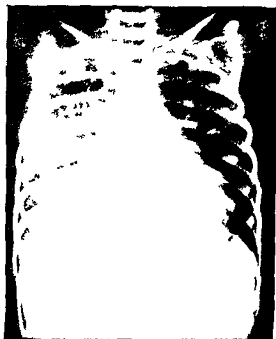


Fig 217—Interventricular septal defect or maladie de Roger The heart appears to be enlarged more than it actually was because this was a bedside film (weight of heart at necropsy was 113 gm) Death was due to pneumonia The slight resemblance to mitral configuration is normal for children The electrocardiogram was essentially normal *

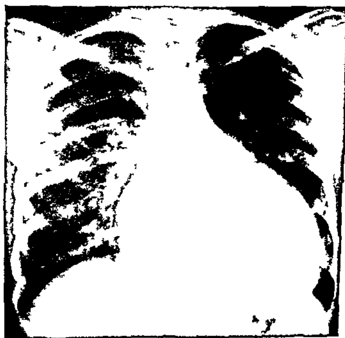


Fig 218—Patent ductus arteriosus Prominent conus shadow and hypertrophied left ventricle should be noted Diagnosis confirmed at operation

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CHAPTER 43

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INTRODUCTION CONGENITAL ABNORMALITIES

Circulatory Phenomena Associated with Systemic Derangements
Congenital Cardiovascular Disease
Congenital Arteriovenous Fistula
Simple Lymphangioma
Cavernous Lymphangioma
Cystic Lymphangioma (Hygroma)
Lymphadenocele

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ETIOLOGY

The causes for the development of congenital cardiovascular disease are unknown When the complicated mechanism required to construct the

Isolated Pulmonary Stenosis —Isolated pulmonary stenosis causes the development of *cyanosis* in the later years of life It is associated with a harsh *systolic murmur* over the pulmonic area best transmitted toward the left shoulder the second pulmonic sound may be diminished or normal Often a diastolic pulmonary insufficiency murmur of the type of a *Graham Steell* can be heard

Fluoroscopy usually reveals considerable *enlargement of the right ventricle* the electrocardiogram often shows *right axis deviation*

Differential Diagnosis —See p 964

Subacute bacterial endocarditis (p 1021) occurs frequently the remaining patients develop *circulatory deficiency* (p 941)

Dextrocardia —Dextrocardia may occur as an isolated lesion or it may represent a manifestation of complete or partial *situs inversus* The disturbance causes no symptoms and the patient has a normal life expectancy The electrocardiogram reveals inversion of Lead 1 with transpositions of Leads 2 and 3 (ECG 81)

Congenital Valve Defects —In addition to pulmonary insufficiency and stenosis bicuspid valves may be encountered at the aortic and pulmonary orifices In themselves these abnormalities have no importance except that they provide places of least resistance for the later development of a *subacute bacterial endocarditis* (p 1021)

See *Lutembacher s Disease* (p 956)

Tetralogy of Fallot —The tetralogy of Fallot consists of an interventricular septal defect pulmonary stenosis an overriding aorta and right ventricular hypertrophy

The patient with the tetralogy of Fallot is *cyanotic* at birth since venous blood reaches the systemic circulation through the overriding aorta *polycythemia* and *clubbing of the fingers* are present a loud *systolic murmur is usually audible over the pulmonic area Fluoroscopy shows* the characteristic *sabot (wooden shoe) configuration* due to *right ventricular enlargement* The electrocardiogram reveals marked *right axis deviation* *Differential Diagnosis* —See p 964

The tetralogy of Fallot is the most frequent cyanotic lesion and may be associated with heart failure (p 941) There is an occasional superimposition of *subacute bacterial endocarditis* (p 1021) or the development of *pulmonary tuberculosis* (p 2199) Surgical therapy by the production of a shunt from a systemic to the pulmonary artery is now feasible in expert hands

Eisenmenger s Complex —Eisenmenger s complex resembles the tetralogy of Fallot There is dextroposition of the aorta an interventricular septal defect hypertrophy of the right ventricle and enlargement of the pulmonary artery Systolic murmurs are heard all over the pulmonic area There *is right axis deviation and the heart shape is as in the tetralogy of Fallot* except that the pulmonary artery is prominent (p 964) Surgical therapy as in the tetralogy of Fallot may be feasible

CLINICAL MANIFESTATIONS IN CONGENITAL CARDIAC DISEASE

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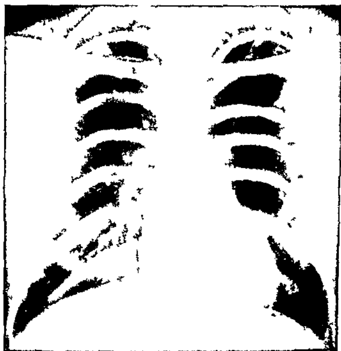


Fig 219—Coarctation of the aorta showing lack of prominence of aortic knob scalloping of ribs and prominent left ventricle

aorta compresses the esophagus from behind and pushes it forward and to the left

Pulmonary Insufficiency—Insufficiency of the pulmonary valve is a rare congenital lesion that is due to fetal endocarditis The condition is usually recognized only at autopsy since the infant rarely survives

Pulmonary Atresia—Obliteration of the pulmonic orifice is less frequently observed than pulmonary stenosis, next to be described With atresia, the pulmonary artery is small, the ductus arteriosus and the ventricular septum usually remain open as compensatory or accompanying lesions The bronchial arteries furnish collateral circulation The condition is complicated and rarely compatible with survival

TABLE 53.—CIRCULATORY MANIFESTATIONS IN SYSTEMIC DISORDERS (*Continued*)

Etiology	Circulatory Lesions
Myxedema	Myocardial dilatation (p 7 9)
Adrenal cortical excess	Hypertension (p 910) Backward failure (p 941)
Adrenal cortical deficiency	Hypotension (p 916) Forward circulatory failure (p 920)
Menopause	Tendency to essential hypertension (p 900)
Toxemias of pregnancy	Tendency to essential hypertension (p 900)
Avitaminoses	Beri beri heart (p 1014) Dilatation (p 2) Backward failure (p 941)
Ergotism	Peripheral vascular spasm and gangrene (p 996)
Obesity	Tendency to hypertension (p 900)
Diabetes mellitus	Tendency to arteriosclerotic change (p 1[illegible]61)
Von Gierke's disease	Congenital idiopathic hypertrophy of the heart (p 19 8)
Anemia	Myocardial and [illegible]bral ischemia (p 98)
Pernicious anemia	As above and myocarditis ([illegible]) (p 1080)
Polycythemia	*Pulmonary arteriosclerosis* (p *994*) Hypertension in lesser circuit Thromboses (p *1123*)
Chronic pulmonary disease	Pulmonary arteriosclerosis (p 994) Hypertension in lesser circuit Cor pulmonale (p 968)
Chronic nephropathies	Hypertension of systemic circuit Heart failure (left) (p 941) [illegible]carditis (p 1008)
Autonomic imbalance	Essential hypertension (p 900) *Neurocirculatory asthenia* (p *89*)
Nicotine poisoning	Possible participant in Hypertension (p 910) Angiospasms (p 1001) Angina pectoris (p 890)

normal cardiac architecture is considered it remains a matter of wonder that defects are not more commonly observed

Many *exciting factors* have been suspected of a predisposing etiologic role The association of congenital cardiac disease with abnormalities of development in other organs and with mental deficiency has led to the suspicion that there is a defective germ plasm A precipitating role has been assigned to all manner of influences including consanguinity maternal frights alcoholism syphilis intrauterine endocarditis secondary to rheu

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Staphylococcus	Acute bacterial endocarditis (p 1020)
Streptococcus	Acute or subacute endocarditis (pp 1020–1021)
Scarlet fever	Endocarditis (p 1016) Nephritis (p 2372) Hypertension (p 910)
Rheumatic fever	Endocarditis (p 1016) Pericarditis (p 1007) Myocarditis (p 1013)
Pneumococcus	Bacterial endocarditis (p 1020) Pericarditis (p 1008) Forward circulatory failure (p 920)
Gonococcus	Bacterial endocarditis (pp 1020–1021) Pericarditis (p 1008)
C diphtheriae	Myocarditis (p 1013) Cardiac arrhythmia (heart block) (p 8 9)
H influenzae	Acute and subacute bacterial endocarditis (pp 1020–1021) Pericarditis (p 1007) Forward circulatory failure (p 920)
M tuberculosis	Pericarditis (p 1009)
B melitensis	Chronic endocarditis (p 970)
V cholerae	Forward circulatory failure (p 920)
Gas gangrene	Forward circulatory failure (p 920)
E typhosa	Myocarditis (p 1015) Forward circulatory failure (p 920)
Syphilis	Myocarditis (p 1015) Aortic insufficiency (p 970) Coronary sclerosis (p 983) Aortitis (p 1025) Aneurysm (p 1026)
Filariasis	Elephantiasis (p 3321)
Trichinosis	Myocarditis (p 1015)
Acromegaly	Cardiac hypertrophy (p 867)
Basophilism	Hypertension (p 910) Cardiac hypertrophy (p 867)
Hyperthyroidism	Tachycardia (p 875) Hypertension (p 910) Cardiac hypertrophy (p 867) Angina pectoris (p 890) Cardiac arrhythmia (p 875) Backward failure (p 941)

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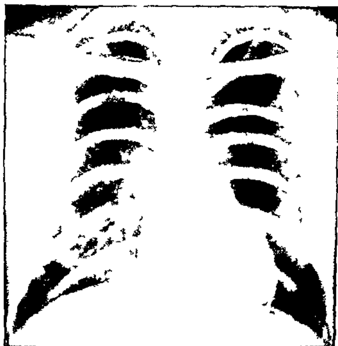


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TABLE 59 —CIRCULATORY MANIFESTATIONS IN SYSTEMIC DISORDERS (*Continued*)

Etiology	Circulatory Lesions
Myxedema	Myocardial dilatation (p 7 2)
Adrenal cortical excess	Hypertension (p 910) Backward failure (p 941)
Adrenal cortical deficiency	Hypotension (p 916) Forward circulatory failure (p 920)
Menopause	Tendency to essential hypertension (p 900)
Toxemias of pregnancy	Tendency to essential hypertension (p 900)
Avitaminoses	Beri beri heart (p 1014) Dilatation (p 7 2) Backward failure (p 941)
Ergotism	Peripheral vascular spasm and gangrene (p 996)
Obesity	Tendency to hypertension (p 900)
Diabetes mellitus	Tendency to arteriosclerotic change (p 1261)
Von Gierke s disease	Congenital idiopathic hypertrophy of the heart (p 19 8)
Anemia	Myocardial and cerebral ischemia (p 98)
Pernicious anemia	As above and myocarditis (tigering) (p 1090)
Polycythemia	*Pulmonary arteriosclerosis* (p 994) Hypertension in lesser circuit Thromboses (p 1123)
Chronic pulmonary disease	Pulmonary arteriosclerosis (p 994) Hypertension in lesser circuit Cor pulmonale (p 968)
Chronic nephropathies	Hypertension of systemic circuit Heart failure (left) (p 941) Pericarditis (p 1008)
Autonomic imbalance	Essential hypertension (p 900) Neurocirculatory asthenia (p 897)
Nicotine poisoning	Possible participant in Hypertension (p 910) Angiospasms (p 1001) Angina pectoris (p 890)

normal cardiac architecture is considered it remains a matter of wonder that defects are not more commonly observed

Many *exciting factors* have been suspected of a predisposing etiologic role The association of congenital cardiac disease with abnormalities of development in other organs and with mental deficiency has led to the suspicion that there is a defective germ plasm A precipitating role has been assigned to all manner of influences including consanguinity maternal frights alcoholism syphilis intrauterine endocarditis secondary to rheu

startling figure of seven to twelve million with 130 to 160 per cent of hemoglobin

Backward Circulatory Failure—Symptoms of backward circulatory failure occur with the more advanced congenital defects the patient develops dyspnea edema hemoptysis epistaxis and ascites

Manifestations of Cerebral Anoxia—With cerebral anoxia neurological symptoms arise they include vertigo faintness syncope delirium mania coma and convulsions The manifestations are usually agonal

Developmental Defects—*The more severe congenital cardiac defects* are associated with stunting of growth (p 693) and defective mentality it is not uncommon to note the coexistence of Mongolian idiocy (p 1165) with congenital cardiac lesions

Cardiac Murmurs and Thrills—The key to the type of congenital defect is occasionally provided by the timing and situation of the cardiac thrill and murmur With the exception of the continuous murmur of patent ductus *arteriosus all others are essentially systolic* (p 964) *presystolic* or diastolic elements may be heard in Lutembacher s Disease (p 956) and pulmonary insufficiency (p 960)

Changes in the Cardiac Silhouette (Fig 119) —Fluoroscopic and roentgenographic evidences assist the diagnosis of congenital cardiac disorders *Right auricle enlargement* is seen in auricular septal defects *right ventricle enlargement* is particularly marked in pulmonary stenosis and the Fallot and Eisenmenger syndromes *left ventricle hypertrophy* characterizes the patent ductus aortic stenosis and coarctation the *pulmonary segment* is prominent in auricular septal defects patent ductus pulmonary stenosis and the Eisenmenger complex

Differential Diagnosis—See p 964

Disturbances in Blood Pressure—The only congenital cardiac lesion with marked disturbance in blood pressure is coarctation of the aorta In this condition there is a hypertension in the upper extremities with normal or low levels in the legs (p 959)

Electrocardiogram (**ECG 23, 79**)—Electrocardiographic tracings are of occasional assistance in diagnosing congenital cardiac defects *right axis deviations are present in the cyanotic* type of abnormalities thus they appear with interauricular septal defects with Fallot s tetralogy Eisenmenger s complex and pulmonary stenosis *Left axis deviation* is present with ventricular septal defects patent ductus subaortic stenosis and coarctation of the aorta In dextrocardia the leads are completely inverted

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of the more complicated congenital cardiac defects requires the assistance of the expert often he is compelled to reserve his decision or alter his opinion as the result of autopsy findings In Table 60 the more obvious manifestations are summarized (p 964)

ASSOCIATED CONDITIONS

Congenital cardiac abnormalities rarely occur as isolated manifestations The patient is therefore examined for evidences of other anomalies within and beyond the circulatory mechanisms

matic fever or syphilis in the pregnant woman malnutrition or exposure to roentgen radiation

It is not possible to make a reasonable case for any of these agencies However it has been shown that rubella (p 417) and rarely measles (p 409) occurring in the first three months of pregnancy may result in cardiac anomalies invariably associated with cataracts With this single exception congenital cardiac defects are entirely unpredictable Parents of a congenital cardiac child need not necessarily anticipate similar disturbances in future progeny they may safely be assured that pregnancy again may be attempted

PATHOGENESIS

An understanding of the variety of congenital cardiac lesions requires a knowledge of the evolution of the cardiovascular system The heart develops from a structure containing a single auricle a single ventricle a single aortic bulb and the vascular arches of the primitive gill clefts in its mature form it possesses two auricles two ventricles an aorta and the pulmonary artery

CLINICAL TYPES OF CONGENITAL CARDIAC DISEASE

Ectopia cordis
Interauricular septal defects Lutembacher s disease
Interventricular septal defects (Roger s disease)
Patent ductus arteriosus (Botalli)
Subaortic stenosis
Coarctation of the aorta
Persistence of the right aortic arch (dysphagia lusoria)
Pulmonary insufficiency
Pulmonary atresia
Pulmonary stenosis
Dextrocardia
Congenital valve defects
Tetralogy of Fallot
Eisenmenger s complex

Ectopia Cordis—A failure of fusion of the thoracic cage results in exposure of the pericardium just beneath the skin The condition is not necessarily associated with clinical manifestations and may be treated by plastic surgical procedures

Interauricular Septal Defects (Patent Foramen Ovale Lutembacher s Disease)—The interauricular septal defect is a very frequent congenital cardiac lesion the septum is deficient the auricular cavities communicate each with the other and in one third of the instances the septal defect is accompanied by a *congenital mitral stenosis* (*Lutembacher s disease*)

The septal defect is suspected in the presence of a harsh systolic decrescendo *murmur* heard best over the pulmonic area and accompanied by a systolic *thrill* The second pulmonic sound is usually accentuated in many instances a pulmonary diastolic murmur also is present systolic and diastolic murmurs also may be audible at the apex Cyanosis if present is transitory

Fluoroscopic examination reveals a marked enlargement of right auricle right ventricle and pulmonary artery the phenomenon of *hilar dance* is observed (Fig 216) The electrocardiogram may be completely normal but more often it shows *right axis deviation* with prominent P waves and an intraventricular conduction defect auricular fibrillation may be encountered

Differential Diagnosis—See p 964

changes Of lesser importance are the disturbances due to circulatory failure which are more or less generic

Cyanosis —Cyanosis is the most striking symptom of congenital cardiac disease So marked is this that the condition has been described as *morbus caeruleus* mothers refer to the afflicted children as *blue babies* The cyanosis may vary from a slight lividity of the face hands and feet to an intense uniform blue discoloration the retina also appears cyanotic

Maude Abbott has utilized cyanosis in order to classify congenital cardiac defects Patients are divided into those who evidence cyanosis those in whom the sign is potentially present and those who are free from cyanosis

The Acyanotic Group —The acyanotic group include those patients in whom there is no shunting of venous blood into the systemic circulation Such lesions include septal defects coarctation of the aorta (p 959) dextrocardia (p 961) patent ductus (p 957) and valve defects (p 970)

The Cyanotic Group (Morbus Caeruleus) —The cyanotic group includes those patients in whom a shunt has resulted in the presence of venous blood in the greater circulation This occurs when blood from the right side of the heart by passes the lungs through an abnormal communication in the auricle ventricle or ductus arteriosus and then enters the left ventricle without having been aerated The cyanotic group also includes those patients in whom there is a mechanical defect resulting in a diminished blood supply to the lungs These conditions exist in the tetralogy of Fallot (p 961) and the Eisenmenger complex (p 961)

The Potentially Cyanotic Group (Tardive Cyanosis) —The potentially cyanotic group includes those patients in whom the venous arterial shunt is inconsequential or transient as in the lesser degrees of septal defect narrow patency of the ductus arteriosus and pulmonary stenosis (p 964)

The transitory attacks of cyanosis occur with disturbances in the normal pressure relationship between the chambers of the heart Usually the pressure in the left chamber of the heart is greater than in the right and the tendency is for a left to right shunt However with an attack of coughing or failure of the left ventricle there is relative increase in the pressure on the right side the shunt is from right to left and paroxysmal cyanosis is observed

Clubbing of Fingers and Toes —Clubbing of fingers and toes occurs in the cyanotic group of congenital cardiac disorders (Fallot Eisenmenger) The condition is conspicuously absent in the acyanotic patient and occurs to a slight degree if at all in the potentially cyanotic group

Dyspnea —A striking feature of the cyanosis of congenital cardiac disease is the relative absence of dyspnea Cyanosis may be of maximal degree with little or no dyspnea other than on exertion So amazing is this observation that the appearance of a cyanotic patient without dyspnea arouses in the mind of the astute practitioner the suspicion that there is present a congenital cardiac abnormality As congestive heart failure develops dyspnea is encountered but the patient gives a clear history of cyanosis long antedating the shortness of breath

Polycythemia —The cyanotic group of patients (Fallot Eisenmenger) exhibit a marked compensatory polycythemia the red cells may reach the

The outlook in interauricular septal defects is variable (p 965) the superimposition of a *subacute bacterial endocarditis* (p 1021) is rare but *right heart failure* (p 941) may occur

Interventricular Septal Defects (Roger s Disease)—The interventricular septal defect is the most frequently discussed congenital cardiac lesion despite the fact that it is rarely observed beyond infancy It is infrequently an isolated lesion and usually is one aspect of a more complicated disturbance

The interventricular septal defect produces a harsh loud systolic *murmur* that is characteristically heard over the third or fourth intercostal spaces to the left of the sternum it is accompanied by a *thrill* The mur

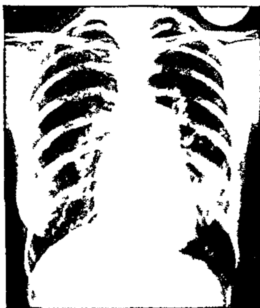


Fig 16—Lutembacher s disease The distinctive silhouette with unusually prominent pulmonary conus and pulmonary vessels should be noted Diagnosis was proved at necropsy

mur is usually transmitted to the apex but is barely heard in the pulmonic areas (Fig 217)

Fluoroscopic examination may show moderate *left ventricular enlargement* but more often there is no observable abnormality The electrocardiogram is normal though it may give some evidence of a *left axis deviation*

Differential Diagnosis—See p 964

Interventricular septal defect is associated with *subacute bacterial endocarditis* in almost a third of all instances the development of circulatory deficiency (p 920) is rare

Patent Ductus Arteriosus (Botalli)—The persistence beyond the first or second year of patency of the ductus arteriosus result in a significant *arteriovenous communication* between aorta and pulmonary artery the blood is shunted from the arterial to the venous side of the circulation

COMPLICATIONS

The functional cardiac conditions that result from a congenital cardiac defect engender the same risks as those of acquired etiology The *hypertension* of coarctation of the aorta is apt to produce the pressure manifestations elsewhere described (p 910) the cyanotic group of defects results in *right ventricular failure* (p 942) with sudden death from cerebral *anoxia* the damaged cardiac structures furnish sites of least resistance for the development of *subacute bacterial endocarditis* (p 1021)

PROGNOSIS

The prognosis in congenital heart disease varies with the lesion and the extent of the deformity The mere presence of a congenital lesion is not necessarily ominous Many autopsies reveal congenital defects unsuspected and undiagnosed during life and compatible with longevity Patients with the tetralogy of Fallot (p 961) may survive into their fiftieth years

The immediate prognosis of the congenital defect is based wholly upon the attendant circumstances In the absence of cyanosis hypertension or a marked alteration in cardiac contour the patient may be given reasonable reassurance provided that his life is led with comparative freedom from excessive strain and infection A guarded outlook is in store for those with cyanosis hypertension or marked alteration in the cardiac silhouette

The long range prognosis of congenital cardiac disease must always bring into consideration the unknown factor of a superimposed *subacute bacterial endocarditis* (p 1021)

TREATMENT

The treatment of congenital cardiac disease is dependent upon the nature of the deformity There need be relatively little modification of the *way of life for the patient who has no obvious cyanosis surgical intervention* by the expert merits consideration in the potentially and obviously cyanotic groups (p 964)

Psychotherapy—Patients with well compensated congenital defects should receive a maximum amount of *reassurance* Within limitations they and their parents may be advised that the span of life need not necessarily be significantly shortened and that reasonably normal activities are permissible

Prophylactic Chemotherapy—The hazard of *subacute bacterial endocarditis* (p 1021) casts its shadow over each patient with a congenital cardiac deformity On this account the prophylactic use of *sulfonamide* (p 88) is recommended as in the management of the patient with *rheumatic fever* (p 186) Infectious diseases particularly of the acute respiratory varieties (p 391) are managed with the utmost conservatism chemotherapy is instituted upon the slightest suspicion of a complicating invasion with streptococci (p 157) or other organisms capable of producing endocardial inflammation preoperative sulfonamide administration is imperative particularly before *tonsillectomy* (p 2038) or *tooth extraction* (p 1664)

Surgery—Ligation of the patent ductus arteriosus (p 957) reconstruction of a coarctation of the aorta and the creation of shunts to the pulmonary artery in the cyanotic groups hold great promise in expert surgical hands



Fig 217—Interventricular septal defect or maladie de Roger The heart appears to be enlarged more than it actually was because this was a bedside film (weight of heart at necropsy was 113 gm) Death was due to pneumonia The slight resemblance to mitral configuration is normal for children The electrocardiogram was essentially normal

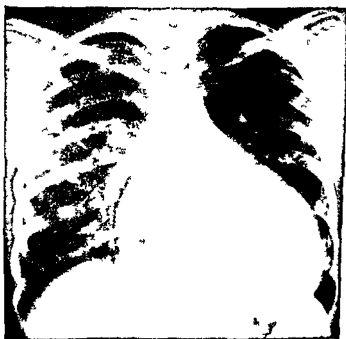


Fig 218—Patent ductus arteriosus Prominent conus shadow and hypertrophied left ventricle should be noted Diagnosis confirmed at operation *

TABLE 60.—MANIFESTATIONS OF CONGENITAL CARDIAC DISEASE

Lesion	Murmur	Site	Cyanosis	Cardiac Contour	Electrocardiogram	Miscellaneous
Auricular Septal Defect	Systolic	Pulmonary	Slight	Prominence of right auricle right ventricle and pulmonary artery	Deviation to right	P_2 accentuated
Lutembacher's Disease	Systolic Pre systolic	Pulmonary apex	Slight	No change	P prominent	Hilar Dance
Ventricular Septal Defect (Roger's Disease)	Systolic	L-3-4	None	Left ventricle may be prominent	Deviation to left	
Patent Ductus Arteriosus (Botalli)	Systolic and dia stolic	L-2	None	Left ventricle and pulmonary ar tery may be prominent	Deviation to left	Low diastolic pressure P_2 ac-centuated Consider surgery
Subaortic Stenosis	*Systolic*	*Aortic area*	None	*Prominence of left ventricle and aorta*	*Deviation to left*	*Low pulse pressure*
Coarctation of Aorta	Systolic	Aortic area	None	Prominence of left ventricle	Deviation to left	Hypertension in arms Con sider surgery
Pulmonary Stenosis	Systolic	Pulmonary area	Late	Prominence of right ventricle and pulmonary artery	Deviation to right	P_2 diminished
Tetralogy of Fallot	Systolic	Pulmonary area	Extreme	Prominence of right ventricle	Deviation to right	Polycythemia clubbing Con sider surgery
Eisenmenger's Complex	Systolic	Pulmonary area	Extreme	Prominence of right ventricle and pulmonary artery	Deviation to right	Polycythemia clubbing P_2 accentuated Consider sur gery

The patency of the ductus arteriosus is usually associated with mental and physical retardation cyanosis is absent systolic and diastolic *machinery murmurs* are heard best over the left second interspace and are transmitted to the jugular the pulmonic second sound is accentuated diastolic blood pressure is low and pulse pressure is increased

Fluoroscopy reveals moderate *left ventricular enlargement* prominence of the pulmonary artery segment the observation of the hilar dance is rare The electrocardiogram is variable a *left axis deviation* is frequent

Differential Diagnosis —See p 964

The patent ductus is accessible to surgery Ligation though hazardous is life saving

The combination of a patent ductus arteriosus with other congenital defects is rare beyond infancy *subacute bacterial endocarditis* (p 1021) may be superimposed and does not contraindicate surgery

Subaortic Stenosis —Subaortic stenosis is not as rare as is generally believed in the experience of the associate editor (A G) it is of more frequent occurrence than interventricular septal defect

The presence of subaortic stenosis is suspected when a harsh loud *systolic murmur* is heard over the aortic area with characteristic transmission to the carotid artery Occasionally the murmur may be of maximum intensity over Erb s area or even over the apex A *vibratory thrill* usually accompanies the murmur it is felt best over the aortic area and the carotid arteries the second aortic sound may be normal or of diminished intensity the pulse pressure is low

Fluoroscopy shows varying degrees of *left ventricular enlargement* there is often a moderate dilatation of the supravalvular portion of the aorta and the electrocardiogram frequently shows *left axis deviation*

Differential Diagnosis —See p 964

A superimposition of *subacute bacterial endocarditis* (p 1021) occurs in about 10 per cent of the patients *Angina pectoris* (p 890) is frequent sudden death may be encountered Circulatory deficiency often develops

Coarctation of the Aorta —An elevation of blood pressure (p 910) during childhood or adolescence gives rise to the suspicion of the presence of a coarctation of the aorta This congenital abnormality is especially probable if there is no demonstrable renal pathology (p 2379)

Coarctation of the aorta with moderate to marked stenosis exists at the beginning of the thoracic portion of the vessel As a result of interference with blood supply nutriment reaches the abdominal organs and the lower extremities through collateral vessels The alteration in circulation results in a considerable *hypertension* in the arms the blood pressure in the legs is low providing pathognomonic findings for the diagnosis of the lesion a *systolic murmur* is heard over the base of the heart as in aortic stenosis (p 971) *bruits* may be audible over the compensatory enlarged intercostals or internal mammaries (Fig 219)

Fluoroscopy reveals a moderate *enlargement of the left ventricle* the aortic knob is not prominent in many instances erosion of the lower borders of the ribs (*scalloping*) is produced by the dilatation of the intercostal arteries The *electrocardiogram* is normal or shows left axis deviation

Differential Diagnosis —See p 964

The *complications* of coarctation of the aorta include the development

CHAPTER 44

ORGANIC DISEASES OF THE CIRCULATORY SYSTEM NEOPLASMS MECHANICAL DISTURBANCES

NEOPLASMS

PRIMARY neoplasms of the heart and pericardium are very rare and occur only as clinical curiosities

Of the Heart—*Rhabdomyosarcomas of the myocardium* are observed in young individuals *myxomas of the auricles* are umors of embryonic origin These lesions are rarely diagnosed except at autopsy and offer no possibility for therapeutic approach

Sarcoma of the Pericardium—Primary pericardial tumors are usually *sarcomatous* they cause compression of the cardiac chambers or vessels and the syndrome of *cardiac tamponade* (p 872) The lesion is rarely recognized until an exploratory operation is performed for the relief of the constrictive pericarditis

Metastatic Carcinomatosis—Metastatic carcinomatous involvement of the pericardium is not unusual it usually produces a secondary *fibrinous pericarditis* (p 1007) with characteristic electrocardiographic changes (p 819) The condition is suspected when a patient with known malignancy develops a pericardial friction rub *Treatment* is symptomatic

Peripheral Growths—Tumors of the peripheral vessels cutaneous vasculature and lymphatics are elsewhere discussed

See *Glomus Tumor* (p 1435) *Vascular Neoplasms of the Skin* (p 3200) *Primary Lymphosarcoma* (p 1137) *Primary Follicular Lymphoblastoma* (p 1137) *Hodgkin s Disease* (*Malignant Lymphoma*) (p 1138) *Metastatic Carcinomatosis* (p 572) *Leukemia* (p 1100)

MECHANICAL DISTURBANCES OF THE CIRCULATORY SYSTEM

The mechanical disturbances of the circulatory system require careful consideration since many are amenable to therapy Cardiac tamponade may be alleviated wounds of the heart may be approached surgically for repair peripheral aneurysms may be ligated the shunt in an arteriovenous aneurysm may be tied off varicose veins can be excised or fibrosed by the injection of irritant chemicals intravascular thromboses may be prevented by the use of the anticoagulants (p 1045) and emboli may be removed surgically through a small incision in the involved vessel

In the following table the more common mechanical disturbances of the circulatory system are summarized

VALVULAR DEFECTS

Valvular defects of the heart are most often the result of a previous attack of *rheumatic fever* (p 186) less often they are on an *arterio*

Antibodies—The antibodies produced by the living cell include anti toxin agglutinin precipitin lysin opsonin complement fixing and neu tralizing antibodies and allergin Hetero antibodies are those developed against the cells of other organisms Iso antibodies react with the cells of the same species such as the iso agglutinins of the human blood groups

Antibodies are probably produced in all of the cells of the body al though the reticulo endothelial system seems to play a dominant part in the process Chemically antibodies are globulins or so closely related to the globulin molecule that their behavior is in large part determined by the reaction of that substance

The manifestations of antibody production may be due to different kinds of antibodies or the same antibody producing different effects Their activities include the neutralization of toxin (antitoxin) agglutination precipitation cellular dissolution increased liability to phagocytosis (opsonin) and sensitization to anaphylaxis (allergin) The presence of antibodies is utilized in diagnostic investigation Serums containing anti body are used in passive immunizations for preventive or curative effects

The Cellular Defenses—The immunity mechanism is greatly enhanced by the cytological phenomenon of *phagocytosis* By this remarkable proc ess bacteria other cells and foreign substances are ingested by the living cells of the host The phagocytic cells include the motile leukocytes of the blood and the fixed cells particularly certain of the connective tissue cells the endothelial cells of the spleen bone marrow and lymphatic glands The latter known as *macrophages* include also the mononuclear leukocytes of the blood and the mobile histiocytes of the connective tissue (the reticulo endothelial system)

The *mechanism of phagocytosis* is quite complicated The contact be tween the phagocyte and its victim is not casual but dependent upon chemical attraction (chemotropism or chemotaxis) Under the influence of opsonin the phagocytes engulf the bacteria Certain micro-organisms survive inclusion in the cellular cytoplasm but others undergo destruc tion and digestion The cellular defenses are stimulated by fortifying the general condition of the patient and by local measures aimed at increasing vascularity

Resistance and Susceptibility—The response of the body to infection is dependent in great part upon immune substances When they are collec tively powerful the organism is either highly *resistant* or completely *im mune* a low titer of immune bodies may result in *susceptibility* The con cept of resistance immunity and susceptibility is one of relativity since no one of these conditions is absolute variations may occur as the result of the operation of a multitude of exogenous and endogenous influences

Types of Immunity—Immunity may be naturally or artificially acquired In either instance resistance may be of the active or passive variety *Natural immunity* is the practitioner s great ally *artificial immunity* repre sents the physician s monumental contribution to preventive medicine Immunity is acquired artificially by the injection of an antigenic agent capable of causing the formation of specific antibodies (*active artificial immunity*) It is also accomplished by the introduction of preformed anti bodies into the tissue fluids (*passive artificial immunity*)

Active immunity is superior to the passive variety since it is more or

form a barrier against bacterial invasion Pathogens exist on the skin and in the body cavities without actually invading the organism it is a common clinical observation that not all who are exposed to the virulent organisms develop manifestations of disease In a typhoid epidemic of water borne etiology a relatively small fraction of the population falls ill and not all of those exposed to venereal infection become afflicted with gonorrhea or syphilis

To what extent is this relative immunity dependent upon mucous membrane integrity? Is it possible that invasiveness results from lesions of lining structures however minute?

Whether or not bacteria can penetrate the unbroken skin or mucous membrane is debatable Certainly an abrasion favors invasiveness and the maintenance and preservation of an unbroken skin or mucous membrane are potent factors in the battle against bacterial invasion The skin and mucosae serve as more than mechanical barriers The former exerts a *bactericidal activity* which may be due to its acidity (pH 5 8 to 5.22) The mucous surfaces in the respiratory passages possess cilia which repel organisms from the accessory sinuses trachea and bronchi The secretions of saliva sweat and tears wash away micro organisms and additionally they contain a *lysozyme* which is active against certain local invaders (p 103)

The Chemical Defenses—Bacterial bodies are exposed to the same digestive processes as other protoplasm The gastric and upper intestinal juices undoubtedly digest swallowed organisms so that the stomach and duodenal contents are usually sterile The tissue juices are also capable of bacterial digestion and interference with bacterial metabolism Of prime importance in this respect are the tissue oxidases and peroxidases It may be that the chemotherapeusis of the *sulfonamides* rests upon an alteration in intermediate tissue or bacterial metabolism resulting in death of the invading organism through processes of altered conditions of oxidation

The Immunologic Defenses—In addition to the nonspecific mechanical and chemical defenses of the body specific immune substances are produced to combat invasion by parasites The immunological mechanism is referred to as an *antigen antibody reaction*

The term antigen is employed to indicate any substance which stimulates the production of specific antibodies The antigens may react with the antibody in an observable way By antibody the immunologist indicates a substance produced by the cells of the host in response to stimulation by an antigen The antibody reacts specifically with its antigen

Antigens—Both the protein and the carbohydrate molecules of invading parasites have antigenic properties The former is the more important in immunology Bacterial products are likewise antigenic the soluble exogenous toxins calling forth the production of a specific antitoxic antibody while the insoluble endotoxin evokes the production of precipitins opsonins agglutinins and other protective substances

Antigenic properties are not limited to living invasive parasites and products Any protein molecule inanimate or animate is capable of antibody production as becomes particularly manifest in the study of allergy where sensitivities exist for such diverse substances as horse serum ragweed pollen foods and drugs The practitioner uses antigen to produce active immunity and for desensitization in the allergic (p 563)

CONGENITAL ARTERIOVENOUS FISTULA

The congenital arteriovenous fistula is a direct communication between artery and vein causing a *venous varix* The lesion is commonest in the *leg* but also occurs in the *arm* and *scalp* In the last named site a *cirsoid aneursym* is noted the lesion produces local heat *bruits* and *thrills* are audible and palpable obliteration by pressure is noted centrally there may be *cardiac hypertrophy* (p 867) and evidences of *backward failure* (p 941)

The shunt is demonstrable by *arteriography* it requires *surgical therapy*

SIMPLE LYMPHANGIOMA

The simple lymphangioma is a collection of lymphatic vessels it forms a soft poorly defined swelling within or just beneath the skin it is easily compressed and is best treated by excision or *electrocoagulation*

CAVERNOUS LYMPHANGIOMA

The cavernous lymphangioma consisting of a collection of dilated lymphatic sinuses forms a smooth protuberance In the early stages the tumor pits on pressure due to the forcing of fluid into the connecting lymphatic ducts, when the condition is more advanced fibrosis appears and the lesion becomes more rigid When it occurs on the *fingers* or the *hands* the part involved may appear greatly thickened This lesion may involve the *tongue* or *lips* causing *macroglossia* (p 1685) or *macrocheilia* (p 1683)

Treatment is unsatisfactory the lesion is not well defined and is difficult to remove *Excision* in stages is probably the best form of therapy *cautery needle coagulation* on numerous occasions may reduce the size of the lesion when it is too extensive for surgical interference

CYSTIC LYMPHANGIOMA (HYGROMA)

The cystic lymphangioma (cystic hygroma) comprises large multilocular lymphatic spaces Occurring most commonly in the *neck* (p 3514) *axilla* (p 3526) or *groin* (p 3092) it is the result of congenital malformation of a primitive lymph sac The condition is entirely benign although in the neck it may produce serious pressure symptoms by spread into the *mediastinum* The growth usually appears in the first year enlarging rapidly It is fluctuant but is not capable of having its fluid completely milked out Rarely it appears first in adolescence

Treatment is *surgical* the operative procedure may be complicated if the lesion involves the mediastinum

LYMPHADENOCELE

The lymphadenocele is characterized by a cystic swelling in clusters of lymph nodes particularly in the groin (p 3092) The condition is not thoroughly understood and may be congenital in origin or secondary to filarial infection (p 3321) Treatment is accomplished by *surgical excision*

stance the diastolic *Graham Steell murmur* becomes audible in the second third or fourth interspaces close to the sternum It is differentiated from the murmur of *aortic insufficiency* by the absence of the peripheral phenomena associated with the latter defect (p 970)

Relative insufficiency of the *tricuspid* orifice is associated with a *systolic* murmur heard in the third fourth or fifth interspace close to the sternal borders Its relative nature is suspected when the sound disappears with improvement in circulatory efficiency

The *Austin Flint* murmur of aortic insufficiency is often deceptive since it is heard at the apex in the period of diastole Its significance is suggested

TABLE 64—PROGNOSIS IN VALVULAR DISEASE

Lesion	Outlook	Danger
Mitral Insufficiency	Excellent	Subacute bacterial endocarditis (p 1091)
Mitral Stenosis	Guarded	Right heart failure subacute bacterial endocarditis auricular fibrillation
Mitral Insufficiency and Stenosis	Guarded	As above
Aortic Insufficiency	Guarded	Left heart failure subacute bacterial endocarditis angina coronary insufficiency
Aortic Stenosis	Fair	As above and forward failure
Aortic Insufficiency and Stenosis	*Fair*	*As above*
Aortic Insufficiency and Mitral Stenosis	Very guarded	As above with failure of both circuits
Pulmonary Insufficiency	Very guarded	Inevitable backward failure
Pulmonary Stenosis	Very guarded	Inevitable backward failure
Tricuspid Insufficiency	Bad	Inevitable backward failure
Tricuspid Stenosis	Bad	Inevitable backward failure

by the absence of the phenomena of mitralization (p 970) and the preponderance of evidence in favor of the aortic defect

Murmurs of Congenital Cardiac Disease—It often requires expert opinion to differentiate between the murmurs produced by congenital cardiac disease and those of rheumatic endocarditis Considerable assistance is provided by the history if the mother states that the murmur was heard at birth

Prognosis—The prognosis of valvular disease is a variable which is dependent in great part upon the incidence of complications These are presented in tabular form in the Table 64

				D	Ai diss				
Apical	t d an t late diastol	Dca	Low p tch d & rumbling	Localized	Qtte p esent	I t se d k I	—	recu.a.c.t	
Left sternal bord r	Early r whol diastol	D phragm or naked ear	Bl wing	Rt. & lt. ternal bord rs & l wer end of sternum	Very are	A rt 2 d lten diminished	Loudest t full expiration	Loud t erect w th p t t leaning forward	Aort regurgitation
C tin us Murmurs									
2 d 2 d lt. interspaces n ar sternum	Thr gh y tol d d ast l	D ll d d phragm	Harsh, loud r in s tole	Ov lefs pper best	by t l nti us	0	Littl change	Littl or o change	P t nt d tus arteriosus
T and Fro Murm									
Precordium	Sy tol and diastol	Ear	R b	I reased by pressure	Yes	No	N ne	Non	Acute fib o us pericarditis

Courtesy of American Heart Assoc ti n, In † Aortic insuffi en y us ally prese t as w ll. ‡ Unless replaced by ystolic murmu

Treatment

The treatment of the patient with a valvular defect is dependent upon the circulatory efficiency of the heart If there is no significant impairment attention is directed mainly at psychotherapy and prophylactic chemotherapy

Psychotherapy —An earnest effort should be made to prevent the devel opment of an anxiety state or cardiophobia in the child or adult who has a mere valvular defect *Reassurance* is a potent weapon of inestimable efficacy The attitude of the practitioner who first hears the cardiac noise may determine whether the future life of his patient will follow a sure and useful course or one beset with fears and apprehensions

The *practitioner who visits the large cardiac clinics finds numerous* adolescents and young adults segregated from their fellows because they have a fairly loud systolic murmur While it is necessary to observe cer tain precautions with these children the psychological damage of segrega tion is great In heart stations or the offices of the cardiologists the children see other youngsters with congestive failure and invalidism and it is inevitable that they should make the inference that some day I will be like that too

Prophylactic Chemotherapy—Prophylactic chemotherapy with the *sul fonamides* is advised the year round in children whose valvular defect is of *rheumatic origin* (p 193) *Luetic cardiacs* are entitled to courses of specific therapy (p 340)

When the patient with a known valvular defect acquires an incidental infection *active chemotherapy* is worthy of consideration even in those diseases which do not necessarily respond to the *sulfonamides* (p 88) or *penicillin* (p 106) For example the common respiratory infection of viral origin is drug resistant yet secondary invasion can be prevented and con trolled by the chemotherapeutic agents which have no effect on the pri mary cause of the disease

Prophylactic chemotherapy is highly advisable in preparation for *ton sillectomy* (p 2038) or *tooth extraction* (p 1663) to prevent the occurrence of a *subacute bacterial endocarditis* (p 1021)

Surgery and Pregnancy in Cardiac Disease —The hazards of surgery and pregnancy in patients with cardiac valvular defects are dependent upon the efficiency of the circulation as elsewhere discussed (p 863)

Surgery —The operation of *valvulotomy* for mitral or aortic stenosis is still in the experimental stage

Congestive Failure —The treatment of congestive failure in the patient with valvular defect is unaffected by the deformity of the orifice The principles are elsewhere considered (p 941)

Measures Not Advocated —It is often as important to stress the nega tive as the positive indications for therapy The mere presence of a mur mur should not lead to the curtailment of useful work reasonable exercise or marriage it does not call for *digitalization* which has the potential for harm if given only because a noise is heard it does not require the ad ministration of *caffeine strychnine epinephrine camphor metrazol* or *coramine* to strengthen the beat

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The congenital arteriovenous fistula is a direct communication between artery and vein causing a *venous varix* The lesion is commonest in the *leg* but also occurs in the *arm* and *scalp* In the last named site a *cirsoid aneursym* is noted the lesion produces local heat *bruits* and *thrills* are audible and palpable obliteration by pressure is noted centrally there may be *cardiac hypertrophy* (p 867) and evidences of *backward failure* (p 941)

The shunt is demonstrable by *arteriography* it requires *surgical therapy*

SIMPLE LYMPHANGIOMA

The simple lymphangioma is a collection of lymphatic vessels it forms a soft poorly defined swelling within or just beneath the skin it is easily compressed and is best treated by excision or *electrocoagulation*

CAVERNOUS LYMPHANGIOMA

The cavernous lymphangioma consisting of a collection of dilated lymphatic sinuses forms a smooth protuberance In the early stages the tumor pits on pressure due to the forcing of fluid into the connecting lymphatic ducts when the condition is more advanced fibrosis appears and the lesion becomes more rigid When it occurs on the *fingers* or the *hands* the part involved may appear greatly thickened This lesion may involve the *tongue* or *lips* causing *macroglossia* (p 1685) or *macrocheilia* (p 1683)

Treatment is unsatisfactory the lesion is not well defined and is difficult to remove *Excision* in stages is probably the best form of therapy *cautery needle coagulation* on numerous occasions may reduce the size of the lesion when it is too extensive for surgical interference

CYSTIC LYMPHANGIOMA (HYGROMA)

The cystic lymphangioma (cystic hygroma) comprises large multilocular lymphatic spaces Occurring most commonly in the *neck* (p 3514) *axilla* (p 3526) or *groin* (p 3092) it is the result of congenital malformation of a primitive lymph sac The condition is entirely benign although in the neck it may produce serious pressure symptoms by spread into the *mediastinum* The growth usually appears in the first year enlarging rapidly *It is fluctuant but is not capable of having its fluid completely milked out* Rarely it appears first in adolescence

Treatment is *surgical* the operative procedure may be complicated if the lesion involves the mediastinum

LYMPHADENOCELE

The lymphadenocele is characterized by a cystic swelling in clusters of lymph nodes particularly in the groin (p 3092) The condition is not thoroughly understood and may be congenital in origin or secondary to filarial infection (p 3321) Treatment is accomplished by *surgical excision*

stance the diastolic *Graham Steell murmur* becomes audible in the second third or fourth interspaces close to the sternum It is differentiated from the murmur of *aortic insufficiency* by the absence of the peripheral phe nomena associated with the latter defect (p 970)

Relative insufficiency of the *tricuspid* orifice is associated with a *sys tolic* murmur heard in the third fourth or fifth interspace close to the sternal borders Its relative nature is suspected when the sound disappears with improvement in circulatory efficiency

The *Austin Flint* murmur of aortic insufficiency is often deceptive since it is heard at the apex in the period of diastole Its significance is suggested

TABLE 64—PROGNOSIS IN VALVULAR DISEASE

Lesion	Outlook	Danger
Mitral Insufficiency	Excellent	Subacute bacterial endocarditis (p 1091)
Mitral Stenosis	Guarded	Right heart failure subacute bac terial endocarditis auricular fibril lation
Mitral Insufficiency and Stenosis	Guarded	As above
Aortic Insufficiency	Guarded	Left heart failure subacute bacterial endocarditis angina coronary in sufficiency
Aortic Stenosis	Fair	As above and forward failure
Aortic Insufficiency and Stenosis	Fair	As above
Aortic Insufficiency and Mitral Stenosis	Very guarded	As above with failure of both cir cuits
Pulmonary Insufficiency	Very guarded	Inevitable backward failure
Pulmonary Stenosis	Very guarded	Inevitable backward failure
Tricuspid Insufficiency	Bad	Inevitable backward failure
Tricuspid Stenosis	Bad	Inevitable backward failure

by the absence of the phenomena of mitralization (p 970) and the pre ponderance of evidence in favor of the aortic defect

Murmurs of Congenital Cardiac Disease—It often requires expert opin ion to differentiate between the murmurs produced by congenital cardiac disease and those of rheumatic endocarditis Considerable assistance is pro vided by the history if the mother states that the murmur was heard at birth

Prognosis—The prognosis of valvular disease is a variable which is de pendent in great part upon the incidence of complications These are pre sented in tabular form in the Table 64

CHAPTER 44

ORGANIC DISEASES OF THE CIRCULATORY SYSTEM NEOPLASMS MECHANICAL DISTURBANCES

NEOPLASMS

PRIMARY neoplasms of the heart and pericardium are very rare and occur only as clinical curiosities

Of the Heart—*Rhabdomyosarcomas of the myocardium* are observed in young individuals *myxomas of the auricles* are umors of embryonic origin These lesions are rarely diagnosed except at autopsy and offer no possibility for therapeutic approach

Sarcoma of the Pericardium —Primary pericardial tumors are usually *sarcomatous* they cause compression of the cardiac chambers or vessels and the syndrome of *cardiac tamponade* (p 872) The lesion is rarely recognized until an exploratory operation is performed for the relief of the constrictive pericarditis

Metastatic Carcinomatosis —Metastatic carcinomatous involvement of the pericardium is not unusual it usually produces a secondary *fibrinous pericarditis* (p 1007) with characteristic electrocardiographic changes (p 819) The condition is suspected when a patient with known malignancy develops a pericardial friction rub *Treatment* is symptomatic

Peripheral Growths—Tumors of the peripheral vessels cutaneous vasculature and lymphatics are elsewhere discussed

See *Glomus Tumor* (p 1435) *Vascular Neoplasms of the Skin* (p 3200) *Primary Lymphosarcoma* (p 1137) *Primary Follicular Lymphoblastoma* (p 1137) *Hodgkin s Disease (Malignant Lymphoma)* (p 1138) *Metastatic Carcinomatosis* (p 572) *Leukemia* (p 1100)

MECHANICAL DISTURBANCES OF THE CIRCULATORY SYSTEM

The mechanical disturbances of the circulatory system require careful consideration since many are amenable to therapy Cardiac tamponade may be alleviated wounds of the heart may be approached surgically for repair peripheral aneurysms may be ligated the shunt in an arteriovenous aneurysm may be tied off varicose veins can be excised or fibrosed by the injection of irritant chemicals intravascular thromboses may be prevented by the use of the anticoagulants (p 1045) and emboli may be removed surgically through a small incision in the involved vessel

In the following table the more common mechanical disturbances of the circulatory system are summarized

VALVULAR DEFECTS

Valvular defects of the heart are most often the result of a previous attack of *rheumatic fever* (p 186) less often they are on an *arterio*

Pathology—The pathology of arteriosclerosis is best illustrated by noting the changes in the elastic coat and intima of the aorta

Changes in the Elastic Coat—The initial pathologic disturbance in arteriosclerosis is probably a loss of the normal resilience of the vessel with fragmentation of the internal elastic lamella The fibers at first appear frayed and disorganized later the muscle fibers become involved and may even undergo necrosis Reduplication of the elastic lamella is a pathological characteristic that results from the appearance of delicate elastic fibers in the newly formed sub-intimal lesion next to be described

Intimal Change—The earliest macroscopic lesions of arteriosclerosis are seen in the intima Slightly elevated and flattened yellow streaks are noted on the posterior wall of the aorta usually between and about the orifices of the intercostal arteries On microscopic examination, the yellow areas are found to be intimal thickenings produced by new formations of connective tissue in which are enmeshed large wandering cells that are heavily fat laden

With advancement in the process the intimal thickening becomes more extensive The tissues undergo hyaline or necrotic change with more abundant accumulation of fatty substance dense connective tissue envelops the fat containing areas which assume a bluish white translucent appearance the lumen of the blood vessel is significantly compromised by encroachment of the newly formed deposits If death occurs in this stage the aorta reveals elevated rounded and irregular plaques which stand up from the intimal surface like firm homogeneous drops of paraffin When sectioned the plaques yield a mass of opaque yellow fatty material whose soft mushy character suggests the name of atheroma (porridge)

Thrombosis and Embolism—In the more advanced stages of arteriosclerosis the atheromatous plaques become dryer and more brittle through impregnation with lime salts cracks and erosions appear in the surrounding intima arteriosclerotic ulcerations are produced the intimal defects invite the development of intravascular thrombi from which small emboli are broken off and thrown into the general circulation

Obliterating Endarteritis—If the intravascular thrombus becomes organized it encroaches further upon the vascular lumen and produces more significant narrowing of the arterial bed with impoverishment of the circulation of the tissues dependent upon the artery for blood supply

Arteriosclerosis is never a strictly localized process quantitative differences are usually revealed The changes may be more marked in the aorta the medium sized vessels the cerebral arteries the coronary branches or the kidneys The degree of change may vary from the yellow discolorations noted in the aorta without the encroachment upon the lumen to a complete obliterating endarteritis in which the lumen is filled with fresh or organized thrombus or heaped intimal thickening

Chemistry—The porridge" that is present in the atheromatous plaques contains crystals of *cholesterin* globules of *fat cholesterin esters calcium* and *magnesium* the lime is most in evidence in the dry plaques which may become osseous with marrow cavities and marrow cells

The chemical evidence suggests a relationship between the atherosclerotic deposit and the metabolism of the lipids Clinical observations confirm this suspicion hardening of the arteries is more extensive in obesity (p 695) it occurs to a relatively minor degree in Chinese whose diet is particularly poor in fats

Pathogenesis—It is our opinion that the development of arteriosclerosis is fundamentally a result of vascular stress and strain With each cardiac systole the arterial wall is required to distend to optimum degree and then recoil both actively and passively the passive element, in the production of changes in the vascular lumen is the elastic tissue active vasoconstriction and vasodilatation are accomplished by muscle layers which are under the control of the involuntary nervous system

The artery which can give with each pulsation responds to the demands made upon it in the manner of a sapling in a gentle breeze in the imperfect vessel with a fibrillated elastic coat or inadequacies of its musculature an attempt is made to cushion each blow by laying down a deposit of "porridge

So long as the atheromatous accumulations are pliable and do not greatly encroach upon the vascular lumen the tissue response is adequate and the patient exhibits no significant functional derangement This observation is verified by the universal appearance of arteriosclerosis in those who have suffered from or succumbed to some wholly extraneous derangement However when the deposits of porridge become so extensive that tissue

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CHAPTER 45

ORGANIC DISEASES OF THE CIRCULATORY SYSTEM
ARTERIOSCLEROSIS

Arteriosclerosis is the process by which the circulatory system ages The man is as old as his arteries

The arteriosclerotic process begins immediately after birth and progresses without reversal throughout the span of life The twilight zone between normality and abnormality is difficult of definition In a sense it is erroneous to regard arteriosclerosis as a disease a degenerative process a metabolic disorder or a reasonable clinical diagnosis In actuality the diagnosis of a significant degree of arteriosclerosis is warranted in clinical practice only when the tempo of the phenomenon is unduly increased It is as if the practitioner were to say that the patient looked older than his given years The condition is more definitively apparent in the presence of a complication such as the rupture or thrombosis of a vessel or gangrene in an area whose blood supply has been interrupted

The problems of arteriosclerosis bear upon the entire range of clinical medicine In some individuals it is a kindly and temperate process that proceeds gracefully from cradle to grave in others, it is a tempestuous phenomenon characterized by violent accidents paralysis of tissue function gangrene hopeless invalidism or sudden death

The practitioner walks with arteriosclerosis every minute of his professional existence For the most part he is unaware through familiarity of the presence of his companion At any time in the course of the vital journey the fellow traveler may become burdensome onerous or murderous the point of attack may be the brain the heart, the peripheral vasculature the kidneys or any other of the body organs and tissues

TABLE 61 —MECHANICAL DISTURBANCES OF THE CIRCULATORY SYSTEM (*Continued*)

Lesion	Etiology	Manifestations
Arteriovenous aneurysms	Congenital traumatic in brachials or popliteals	Continuous murmur over lesion artery dilated vein pulsates venous engorgement and redness peripheral to lesion increase of venous return to heart enlargement of left ventricle backward failure may rupture or develop vegetations of subacute bacterial endarter t s (Relieved by local operation)
Dilatation of pulmonary artery	Cor pulmonale interatrial septal defect	Hypertension of lesser circuit right heart failure
Thrombosis	See p 1123	See p 1123
Embolism	See p 1124	See p 1124
Peripheral vascular disease	Arteriosclerosis thromboangitis obliterans Raynaud s disease thrombosis embolism	Interm ttent claudication pain changes in color trophic disorder reactive hyperemia (oscillometry)
Varicose veins	Intra abdominal pre ure congenital val e weakness pregnancy phlebitis	See Minor Sur ery (p 3939)
Varicocele	Stasis	See Diseases of the Male Reproductive Syst m (p 2433)
Hemorrhoids	Constipation portal hypertension increased intra abdominal pressure	See M nor Su gery (p 3946)
Elephantiasis of arms	Following radical mastectomy filariasis (p 3321)	Lymphedema of arms
Elephantias s of legs scrotum or vulva	Surgical nephrit c nephrot c filarial inc eased intra abdominal pressure with malignancy asc tes or caked pelvis follow ng milk leg and recurrent phleb t s congenital i Milroy s disease	Ev dence of hypoproteinemia (Do renal funct on studies search for fila ia Banc ofti) (p 3321)
Obstruction of the thoracic duct	Med astinal lymphadenopathy (tuberculous carcinomatous or Hodgkin s disease) mediastinal tumors filariasis bilharziasis aortic aneurysm accidental surgical ligation	Chylous asc tes chylothorax chyluria

interest They were regarded as of essential diagnostic and prognostic importance children were kept in bed because they had leaking hearts

on the basis that, in the first instance, the vessel changes are the result of wear and tear while in the sedentary the arterial thickening results from hyperalimentation obesity and a higher fat diet. He who would avoid the early development of arteriosclerosis must pursue a course of moderation

Clinical Manifestations — Arteriosclerosis in and of itself rarely produces clinical manifestations The statement that an individual has hardening of the arteries has no real meaning despite its ominous implication Each of us suffers from arterial change the disturbance is of clinical importance only when the tempo of the process is accelerated (*presenile sclerosis*) when the total economy suffers from inadequacy of the blood supply (*generalized arteriosclerosis*) when the vascular change has occurred with excessive rapidity in some special branch of the circulatory tree (coronary sclerosis cerebral arteriosclerosis nephrosclerosis or peripheral arteriosclerosis) with a vascular accident in the nature of a rupture of a brittle vessel or an intravascular thrombosis

Physical Examination —The general practitioner who lives his life with his patients has the opportunity of noting arteriosclerotic changes many years before significant tissue damage occurs Few accomplishments are as little appreciated as the prevention of further vascular injury when intelligent cooperation is secured from the patient whose physician has noted the small signs of impending difficulty

The Small Signs —The early lesions of arteriosclerosis are noted in the temporal and radial vessels the blood pressure and the retinal arteries The sclerotic *temporal artery* appears more prominent it is thickened and of increased tortuosity palpation of the *radial* while often deceptive confirms the impression that the vessel walls are less delicate than the expectancy In the early stages there may not be an absolute hypertension (p 900) but the *pressure gradient* (p 904) is definitely on the rise the systolic level may only increase from the region of 120 to 150 but that change is sufficient to indicate a trend which may be of vital significance

Ophthalmoscopy —By far the most important information is obtained through the ophthalmoscope (p 3628) Visualization of the *retinal vessels* furnishes information that far transcends the value of all other physical and laboratory data In the early stages of arteriosclerosis the arteries first appear narrowed the light reflex is increased the caliber is decreased the course of the vessels is more tortuous the lumen appears irregular in places and the veins are slightly indented at the arterial crossings

Diagnosis —The early diagnosis of significant arteriosclerosis is based upon increase in the gradient of blood pressure and the changes observed in the retinal arteries By the time the more obvious manifestations (p 981) are observed inestimable damage has been done and therapy holds little promise

Course —The course of arteriosclerosis is irresistibly and inevitably progressive The tempo may be gradual or sudden the progress of events may be interrupted by accidents and complications (p 983)

Treatment —The treatment of arteriosclerosis is aimed entirely at prevention of further damage and the attempt to slow the progress of the difficulty

The details of management do not differ from those employed in the regimen used for the control of essential hypertension (p 911) Changes

TABLE 61 —MECHANICAL DISTURBANCES OF THE CIRCULATORY SYSTEM

Lesion	Etiology	Manifestations
Hemopericardium	Trauma hemorrhagic diatheses	Increased area of cardiac dulness cardiac tamponade (p 8 2)
Hydropericardium	Rheumatic fever backward failure	Same as above (Responds to salicylates Clear fluid on aspiration)
Wounds of heart, incised or penetrating	Trauma	Hemopericardium (Treatment surgical)
Contusion of heart	Nonpenetrating lesion steering wheel injury	Hemopericardium (treatment surgical) cardiac arrhythmia
Cardiac tamponade	See p 872	See p 8/2
Valvular defects	See Table 62	See Table 6?
Cor bovinum	Increased tension in greater circuit	Prominence of aortic knob enlargement of left ventricle
Cor pulmonale	Increased tension in lesser circuit (p 919)	Prominence of infundibulum right auricle and right ventricle black cardiacs clubbing of digits
Aneurysm of left ventricle	*Following myomalacia*	*Expansile localized area of heart embolic phenomena from loosening of mural thrombi in onion skin clot rupture and sudden death*
Kyphoscoliotic heart disease (p 3061)	Curvature of spine	Displacement of heart compression of great vessels cor pulmonale and circulatory deficiency
Dilatation of aorta	Arteriosclerosis syphilis	Loss of elasticity with generalized increase of lumen
Aneurysm of aorta (p 1026)	Syphilis arteriosclerosis	Localized expansile dilatation pressure on trachea and larynx paralysis of recurrent laryngeal nerve erosion of vertebral bodies Horner s syndrome
Cerebral aneurysm	Arteriosclerotic or congenital in circle of Willis	Subarachnoid hemorrhage (p 1445)
Other aneurysms	Usually syphilitic but may be mycotic or from periarteritis nodosa most often in males	Innominate subclavian brachial femoral or popliteal arteries Consider surgery particularly with arterio-venous shunts

sclerotic basis (p 976) and in a few instances they are the result of *congenital abnormalities* (p 953)

In the era when physicians were primarily interested in cardiac auscultation the murmurs created in the circulatory pump caused widespread

nutrition is impaired clinical manifestations are registered with calcification drying and ulceration of the plaques the local site suffers from thrombus formation or an actual rupture of continuity with hemorrhage

Predisposing and Exciting Factors in the Production of Arteriosclerosis.—Many factors contribute to the development of arteriosclerosis once the process has been initiated these include psychogenic physical and chemical provocations

Stress and Strain of Civilization—The increasing tempo of modern existence furthers the earlier development and *progression of arteriosclerosis In institutions devoted to the problems* of chronic disease males are admitted almost a decade sooner than the females attesting to their premature vascular breakdown as the result of greater exposure to external conflicts In any community widows predominate the disproportion being due to the greater male toll resulting from accidents directly or indirectly related to arteriosclerosis

Heredity—The practitioner observes many families in whom presenile sclerosis appears as a recurring theme in other families there is remarkable freedom from vascular change with longevity barring accidents

Diet—Lay opinion to the contrary the *high protein diet* does not contribute to the development of arteriosclerosis the Eskimo who subsist almost exclusively on animal protein have no unusual incidence of arteriosclerosis The role of *salt* similarly has been over emphasized a high intake of sodium chloride will not produce arteriosclerosis and a diet deficient in salt will not alleviate the condition once it has be n initiated

The most important dietary element relative to the problems of arterial disease is *fat* The Chinese who rarely can afford fatty substances in their diet, infrequently develop coronary artery disease for example on the other hand obesity is a potent contributing factor in the arteriosclerotic process

Hypertension—Hypertension and arteriosclerosis enjoy a synergistic relationship hypertension (p 900) tends to increase the production of arteriosclerotic changes arteriosclerosis favors elevation of blood pressure

Intoxications—It is very difficult to estimate with accuracy the importance of intoxications in the genesis of arteriosclerosis *lead poisoning* is now so infrequent as to be of only historical importance *alcoholism* once regarded as a potent agency in the development of arterial change seems of decidedly lesser significance since so many drunkards *reveal remarkably delicate vessels Intestinal auto intoxication (p 383) can scarcely be* regarded as a serious factor in arterial disease else it would be more common in women who are almost habitually constipated

The relationship of *tobacco* to arterial disease is much disputed The range of opinion varies between those who are convinced that smoking is a prime cause of arteriosclerosis and those who regard it as of inconsequential significance Our own views were based on two clinical observations which seem pertinent (1) We cannot attribute a vast importance to smoking in the genesis of arteriosclerosis since there has been relatively slight increase in the disease in women who have taken up with Lady Nicotine only in the past thirty years (2) Despite the negative evidence with regard to the generic problem we are convinced that a certain number of susceptible individuals develop vascular disease as the result of smoking and that they are benefited when the habit is abandoned This abnormal sensitivity is no different than is sensitivity to other drugs and chemical substances

Endocrinopathies—Arteriosclerosis is more common in patients who suffer from *hyperthyroidism* (p 1197) this is more in the nature of a work hypertrophy than from increase in circulating hormone Arteriosclerosis seems also to accompany the male and female *climacteric* in all likelihood the association is coincidental rather than that either one of these conditions initiates the other

Nephropathy—The hypertension that accompanies *renal disease* (p 23 0) results in acceleration of the arteriosclerotic process Since arteriosclerosis may produce renal insufficiency the combination of circumstances augurs ill for the afflicted individual

Syphilis—The importance of syphilis in the production of arteriosclerosis seems greatly exaggerated the incidence of Wassermann positivity is no greater in arteriosclerotics than in non-sclerotics

Cardiovascular syphilis (p 1025) which is encountered in a fair proportion of the infected who have received inadequate therapy constitutes a separate *and distinct clinical* entity It is not to be confused with the arteriosclerotic change to which all flesh is heir

Muscular Activity—Arteriosclerotic changes seem to be more intensely developed in manual laborers and those who are completely sedentary This seeming paradox is explicable

TABLE 63—CLASSIFICATION OF MURMURS

Point of Maximal Intensity	Position in Cycle	Preferred Method of Auscultation	Character	Transmission	Assoc. with Thrill	Change of Heart Sounds	Relation to Respiration	Relation to Position	Diagnosis
Important Systolic Murmurs									
Apical	Throughout systole	Bell & diaphragm	Harsh	Toward axilla	Very rare	1st sound often diminished or masked	Usually somewhat less intense with full inspiration	Little or no change	Mitral regurgitation
Aortic			Often loud	Toward neck	Often present	Aortic 2nd diminished or absent†			Aortic stenosis
Aortic			Blowing or mod. harsh	Vessels of neck	0	Aortic 2nd often increased	Little change		Dilatation or atheroma of aorta
Base pulmonic				Heard widely over left upper chest	Often present	Pulmonic 2nd may be accentuated or diminished	Usually less intense with full inspiration		If associated with cyanosis and clubbing—pulmonic stenosis
To the left of mid-sternum			Loud, very harsh		Always present	0	0	0	Interventricular septal defect
Unimportant Systolic Murmurs									
Lower precordial or apical	Early or mid-systole		Blowing, harsh	Localized	0	0	Variable, may disappear during inspiration or expiration	Variable and may disappear	Cardio-respiratory unexplained
Pulmonic	Throughout systole		Blowing or mod. harsh	May be heard over upper precordium	0	0	Less intense disappears with inspiration		Physiological
Diastolic Murmurs—Always Important									
Apical	Mid and late diastole	Bell	Low pitched & rumbling	Localized	Often present	1st sound loud‡	Little change	Louder recumbent	Mitral stenosis
Left sternal border	Early or whole diastole	Diaphragm or naked ear	Blowing	Rt. & lt. sternal borders & lower end of sternum	Very rare	Aortic 2nd often diminished	Loudest at full expiration	Loudest erect with patient leaning forward	Aortic regurgitation
Continuous Murmurs									
2nd or 3rd lt. interspaces near sternum	Throughout systole and diastole	Bell and diaphragm	Harsh, loud in systole	Over left upper chest	Systolic or continuous	0	Little change	Little or no change	Patent ductus arteriosus
To and Fro Murmurs									
Precordium	Systole and diastole	Ear	Rub	Increased by pressure	Yes	No	[illegible]	[illegible]	Acute fibrinous pericarditis

Courtesy of American Heart Association, Inc. † Aortic insufficiency usually present as well. ‡ Unless replaced by systolic murmur.

with the nonluetic variety of arteriosclerosis the *xanthines* accomplish nothing despite the vigorous promotion of drugs such as aminophylline injections of *estrogen* and *androgen* have no influence on the fundamental process so far as our experience is concerned Neither *sour milk* nor the *B bulgaricus* have added to the longevity of our patients

Generalized Arteriosclerosis

The course of a generalized arteriosclerosis is much like that of Oliver Wendell Holmes One Hoss Shay which at the end of one hundred years of service showed

> A general flavor of mild decay
> But nothing local as one may say
>
> It went to pieces all at once—
> All at once and nothing first,
> Just as bubbles do when they burst."

Clinical Manifestations—In a generalized arteriosclerosis the early clinical manifestations (p 979) become more prominent The *temporal vessel* is more tortuous the *radial pulse* feels thicker the *blood pressure* rises to the level of absolute hypertension (p 904) the *retinal vessels* appear so sclerotic that in places the channel is obliterated the *left ventricle* undergoes hypertrophy The *urine* contains a little albumin and an occasional cast the *skin* appears somewhat dryer and of a yellower hue *Cerebration* slows somewhat the memory of recent events is somewhat impaired *personality changes* (p 1359) are noted in that the retiring become more seclusive and the expansive become increasingly garrulous Body weight falls the appetite is lessened somnolence is noted in the daytime and nocturnal sleep is interrupted by the necessity for urination

The hair turns grey and then white *Arcus senilis* appears and becomes increasingly evident eyesight fails through progressive *presbyopia* (p 1537) *tearing* (p 1525) becomes a constant nuisance and *chronic conjunctivitis* gives the bleary appearance of age The *teeth* decay and *dentures* are required Female breast tissue atrophies loss of the fat deposits under the chin and in the abdominal wall causes the flesh to hang down in ugly wrinkles The peripheral musculature becomes flabby and strength is diminished The joints lose their flexibility as best illustrated by the necessity for taking small tottering steps Failure of the peripheral vasculature leads to coldness of hands and feet requiring constant bundling up

Course—The course of the generalized arteriosclerosis is progressive Usually there is the interruption of some complication such as cerebral thrombosis or hemorrhage (p 1439) an acute coronary closure (p 983) or disturbances in the extremities due to obstruction of a peripheral artery (p 995) again the patient progresses to the stages of circulatory deficiency (p 920) or a hypostatic pneumonitis (p 2086) furnishes the last act in the drama

Treatment—The treatment of a generalized arteriosclerosis is wholly directed at prevention of complications and attempts to slow the tempo of the process as previously described (p 979)

exercise and useful work were curtailed because of the noises that were heard through a stethoscope

The modern era of clinical physiology has been characterized by liberation of the practitioner and his patient from the implications associated with cardiac noises The presence of the murmur attracts attention to the circulatory mechanism but it is not permitted to alter the way of life (p 3753) unless accompanied by evidences of active infection or impending circulatory deficiency

The following table summarizes the etiologic factors characteristic murmurs and associated signs and the blood pressure and electrocardiographic changes that are commonly encountered with the various valvular defects

Complications —The patient with valvular defect faces many jeopardies The damaged leaflet may prove to be the origin of a *subacute bacterial endocarditis* (p 1021) *circulatory failure* (p 941) is likely to occur with major defects such as mitral stenosis and aortic insufficiency In the mitralized heart the mechanical breakdown is in the right circuit (p 942) in aortic insufficiency it is the left heart (p 941) that fails The mitralized heart is often associated with the development of a *cardiac arrhythmia* most often a permanent auricular fibrillation (p 886) *Embolizations* (p 1124) are encountered with stenotic lesions

In times of excessive stress patients with mitral and aortic disease and a low cardiac output tend to develop *forward failure* with syncope (p 921) or shock (p 928) Occasionally they evidence the manifestations of myocardial ischemia as revealed by an attack of *angina pectoris* (p 890) or *acute coronary insufficiency* (p 895) In the latter instance *myocardial infarction* (p 983) may be secondarily imposed In the aortic heart there is inevitably some degree of *coronary arteriosclerosis* with the hazard of an *acute coronary closure* (p 983) A considerable number of rheumatic subjects reach the age in which arteriosclerotic heart disease (p 970) and hypertension (p 900) are superimposed on the infectious defect each lesion aggravating the other

Differential Diagnosis —Cardiac murmurs may be produced by conditions other than organic defects of the valves Auscultatory abnormalities may be noted in the normal heart over a normal valve in a damaged heart and in congenital cardiac disease

Abnormal Sounds in the Normal Heart —The presence of the *third sound* at the apex may be confused with the stenotic murmur of mitral disease (p 973) Its true connotation is appreciated by the difference in the quality of the sound absence of the thrill and the normal configuration of the cardiac silhouette In the presence of serious doubt a *phonocardiogram* (p 801) is warranted to settle the matter

Functional murmurs in the normal heart are almost invariably systolic in their timing they are most often apical and are rarely transmitted for any appreciable distance They are not associated with changes in the cardiac silhouette or the electrocardiogram Often they are transitory and they are not associated with subjective symptomatology unless the patient has been given an anxiety neurosis (p 1347)

Functional Murmurs in the Diseased Heart —The damaged heart may develop evidences of pulmonic or tricuspid insufficiency In the first in

are made in the way of life extreme tensions and strains are eliminated *a low calory diet* is ordered for weight reduction (p 669) In the presence of hypothyroidism the basal metabolic rate is raised and then maintained near the normal level by the use of *thyroid extract* (p 1189) hyperthyroidism is treated with *iodides* and *subtotal excision of the gland* *Smoking* is forbidden (p 3884) but the moderate use of *alcohol* is encouraged (p 3847)

DIFFERENTIAL DIAGNOSIS OF

Febrile Disorders of the Aged

Febrile disorders are frequently masked in the aged the debilitated and in those who suffer from chronic disease At times the oversight is due to failure to take temperatures but again grave infections may so overwhelm the patient that a febrile response is simply not demonstrable It is for this reason that the medical attendant in charge of those with feeble resistance *must perform* repeated examinations particularly of unsuspected areas

CAUSE	DIAGNOSTIC FEATURES
Metabolic	Starvation and dehydration
Pharmacologic	Drug fevers with sulfonamides (p 94) and arsenicals (p 116) Following infusions and *transfusions (p 3775)*
Respiratory	Lobar pneumonia acute and chronic pneumonitis lipoid pneumonia and hypostasis Get x ray of chest
Cardiovascular	Silent coronary occlusion ingravescent cerebral thrombosis terminal endocarditis peripheral thrombophlebitis backward failure Get ECG and blood cultures Examine legs and bases of lungs
Urinary	Retention of urine cystitis or pyelitis particularly after catheterization Percuss hypogastrium Urinalysis
Digestive	Constipation impaction of feces dilatation of stomach paralytic ileus subacute or chronic intestinal obstruction or terminal peritonitis Percuss epigastrium and do rectal examination
Hematologic	Progressive anemia and terminal bacteremia (p 53) Get hemogram and blood culture
Tegumentary	Decubitus ulcer Erysipelas (p 167) Examine back and perineum
Peripheral Vascular Disease	Particularly ulcer and gangrene of toes With phlebitis (p 1124)
Wound Infection	*Often with dehiscence (p 4006)*

Sufficient *muscular exercise* is advised to prevent the patient from becoming flabby (p 3757) but excesses are avoided *rest periods* (p 3755) and *cure days* (p 3755) are encouraged leisurely *holidays* (p 3761) and pleasurable *vacations* (p 3761) are potent therapeutic remedies The wealthy may indulge themselves *in climatotherapy or residence at a spa* (p 3765)

Drug therapy accomplishes little or nothing in arteriosclerosis The use of *iodides* harks back to the days when syphilitic endarteritis was confused

TABLE 63.—CLASSIFICATION OF MURMURS

Point of Maximal Intensity	Position in Cycle	Preferred Method of Auscultation	Character	Transmission	Assoc. with Thrill	Change of Heart Sounds	Relation to Respiration	Relation to Position	Diagnosis
Important Systolic Murmurs									
Apical	Throughout systole	Bell & diaphragm	Harsh	Toward axilla	Very rare	1st sound often diminished or masked	Usually somewhat less intense with full inspiration	Little or no change	Mitral regurgitation
Aortic			Often loud	Toward neck	Often present	Aortic 2d diminished also†			Aortic stenosis
Aortic			Blowing or mod. harsh	Vessels of neck	0	Aortic 2d often increased	Little change		Dilatation or atheroma of aorta
Rare pulmonic				Heard widely over lt. upper chest	Often present	Pulmonic 2nd may be accentuated or diminished	Usually less intense with full inspiration		If associated with cyanosis and clubbing—pulmonic stenosis
To the left of mid-sternum			Loud very harsh		Always present	0	0	0	Interventricular septal defect
Unimportant Systolic Murmurs									
Low precordial or apical	Early or mid-systole		Blowing harsh	Localized	0	0	Variable, may disappear during inspiration or expiration	Variable and may disappear	Cardiorespiratory or unexplained
Pulmonic	Throughout systole		Blowing or mod. harsh	May be heard over upper precordium	0	0	Less intense or disappears with expiration		Physiological
Diastolic Murmur—Always Important									
Apical	Mid and late diastole	Bell	Low pitched & rumbling	Localized	Often present	1st sound loud‡	Little change	Loud recumbent	Mitral stenosis
Left sternal border	Early or whole diastole	Diaphragm or naked ear	Blowing	Rt. & lt. sternal borders & lower end of sternum	Very rare	Aortic 2d often diminished	Louder at full expiration	Louder erect with patient leaning forward	Aortic regurgitation
Continuous Murmurs									
2nd or 3rd lt. interspaces near sternum	Throughout systole and diastole	Bell and diaphragm	Harsh, louder in systole	Over left upper chest	Systolic or continuous	0	Little change	Little or no change	Patent ductus arteriosus
To and Fro Murmur									
Precordium	Systole and diastole	Ear	Rub	Increased by pressure	Yes	None	None	None	Acute fibrinous pericarditis

Courtesy of American Heart Association.

† Aortic insufficiency usually present as well.

‡ Unless replaced by systolic murmur.

The presence of arteriosclerotic valvular distortion has more acoustical than functional significance

The *treatment* of arteriosclerotic valvular defects is wholly symptomatic

CORONARY SCLEROSIS

Arteriosclerosis of the coronary arteries has the most ominous implication because of the dependency of the myocardium on these vessels for adequate oxygenation In the order of their gravity the clinical manifestations of coronary arteriosclerosis are *angina pectoris* (p 890) *acute coronary insufficiency* (p 895) and *coronary artery occlusion* (p 983) These may result in *myocardial infarction* (p 984) *fibrosis of the myocardium* (p 993) *myomalacia* (p 992) or *aneurysmal dilatations of the ventricle* (p 993)

ANGINA PECTORIS

The inclusion of the discussion of angina pectoris in the section on Pathologic Physiology (p 890) is intended to emphasize the reversible nature of the myocardial anoxia

ACUTE CORONARY INSUFFICIENCY

As in the instance of angina pectoris acute coronary insufficiency is discussed in the section of Pathologic Physiology (p 895) again in order to stress the remediable aspects of the extracardiac precipitating factors This listing seems justified because of the therapeutic implications and despite the fact that the functional insufficiency may result in myocardial infarction of demonstrable morphologic nature (p 984)

ACUTE CORONARY ARTERY OCCLUSION

Acute occlusion of a coronary artery may result from an intravascular thrombus rupture of a branch with compression due to the extravasated blood or mechanical plugging by an atheromatous plaque or embolization

Irrespective of the nature of the coronary occlusion the presenting symptoms depend upon the effect on the local area of myocardium that is supplied by the involved vessel In an acute closure the myocardium may become infarcted from this accident there may be recovery necrosis or scar tissue replacement of the muscle fibers

Etiology —The importance of the immediate precipitating causes in coronary artery occlusion has mostly medicolegal implications We doubt that an acute episode can be initiated in a normal vessel by unusual strain or trauma but we are of the definite opinion that the sclerotic vessel may be affected by precipitating factors Thus rupture of a subendothelial clot into the lumen of a vessel a rent in the intima or disturbance of an atherosclerotic plaque may well be followed by a closure the episode may be immediate or followed by a period of latency Since the circumstances are not capable of reproduction in the experimental animal the sequence of events remains conjectural but they are most suggestive in many clinical histories A recent report lists 80 fatal occlusions in soldiers between the ages of 20 and 36 years 91 per cent of these

Antibodies—The antibodies produced by the living cell include anti toxin agglutinin precipitin lysin opsonin complement fixing and neu tralizing antibodies and allergin Hetero antibodies are those developed against the cells of other organisms Iso antibodies react with the cells of the same species such as the iso agglutinins of the human blood groups

Antibodies are probably produced in all of the cells of the body al though the reticulo endothelial system seems to play a dominant part in the process Chemically antibodies are globulins or so closely related to the globulin molecule that their behavior is in large part determined by the reaction of that substance

The manifestations of antibody production may be due to different kinds of antibodies or the same antibody producing different effects Their activities include the neutralization of toxin (antitoxin) agglutination precipitation cellular dissolution increased liability to phagocytosis (opsonin) and sensitization to anaphylaxis (allergin) The presence of antibodies is utilized in diagnostic investigation Serums containing anti body are used in passive immunizations for preventive or curative effects

The Cellular Defenses—The immunity mechanism is greatly enhanced by the cytological phenomenon of *phagocytosis* By this remarkable proc ess bacteria other cells and foreign substances are ingested by the living cells of the host The phagocytic cells include the motile leukocytes of the blood and the fixed cells particularly certain of the connective tissue cells the endothelial cells of the spleen bone marrow and lymphatic glands The latter known as *macrophages* include also the mononuclear leukocytes of the blood and the mobile histiocytes of the connective tissue (the reticulo endothelial system)

The *mechanism of phagocytosis* is quite complicated The contact be tween the phagocyte and its victim is not casual but dependent upon chemical attraction (chemotropism or chemotaxis) Under the influence of opsonin the phagocytes engulf the bacteria Certain micro organisms survive inclusion in the cellular cytoplasm but others undergo destruc tion and digestion The cellular defenses are stimulated by fortifying the general condition of the patient and by local measures aimed at increasing vascularity

Resistance and Susceptibility—The response of the body to infection is dependent in great part upon immune substances When they are collec tively powerful the organism is either highly *resistant* or completely *im mune* a low titer of immune bodies may result in *susceptibility* The con cept of resistance immunity and susceptibility is one of relativity since no one *of these conditions is absolute variations may occur as the result* of the operation of a multitude of exogenous and endogenous influences

Types of Immunity—Immunity may be naturally or artificially acquired In either instance resistance may be of the active or passive variety *Natural immunity* is the practitioner s great ally *artificial immunity* repre sents the physician s monumental contribution to preventive medicine Immunity is acquired artificially by the injection of an antigenic agent capable of causing the formation of specific antibodies (*active artificial immunity*) It is also accomplished by the introduction of preformed anti bodies into the tissue fluids (*passive artificial immunity*)

Active immunity is superior to the passive variety since it is more or

less permanent and is accomplished by an ability of the cells to respond quickly and efficiently to the offending agent Its great value lies in the prevention of disease its principal disadvantage is the long latent period required for the development of resistance

NATURAL IMMUNITY

Natural immunity is the resistance to infection that is normally possessed by a species or an individual under normal and natural conditions

Natural immunity is poorly understood It is observed both as a species and an individual variation Thus laboratory workers are familiar with the fact that only certain animals can be infected with certain parasites Experimental investigation of syphilis for instance is limited to chimpanzees monkeys and rabbits

Racial immunities and susceptibilities are also observed Diseases of aliens in the tropics are quite different from those of the natives Explorers and mining engineers fall critically and often fatally ill with malaria and the dysenteries while their less protected native workers apparently are immune perhaps because they have chronic infection or have survived previous attacks

Individual immunities are commonly observed by the practitioner not all of whose patients succumb to exanthems and contagious diseases Certain members of a household fall ill while others living under seemingly similar circumstances remain well despite repeated and massive exposure

ACQUIRED IMMUNITY

Naturally Acquired Active Immunity

In naturally acquired active immunity the patient builds up an immunity as the result of the *development of antibodies* in response to exposure to the living parasite

Relatively complete active immunity follows *smallpox scarlet fever chickenpox mumps measles pertussis typhoid fever cholera yellow fever typhus fever plague* and *poliomyelitis* By contrast there is no significant or lasting immunity conferred by an attack of gonorrhea pneumonia the common cold influenza glanders erysipelas and infections due to the pyogens

Naturally Acquired Passive Immunity

Naturally acquired passive immunity exists as the result of the *passage of antibodies from mother to offspring* through placental transmission or by way of the colostrum and milk Sufficient protective body is present in the newborn infant to defend it against the acute exanthems diphtheria and poliomyelitis for the first few months of its existence

Artificially Acquired Active Immunity

Artificial active immunization is essentially of prophylactic value It constitutes one of the great public health services

Agents Used to Produce Active Immunity—A material that is used to stimulate the production of active immunity must be *antigenic* and relatively harmless Antigenicity denotes that the substance leads to the formation of specific antibodies this specificity is determined by the chemical

Presenile Sclerosis

The cause for the increased intensity of the arteriosclerotic process such as is observed in the presenile scleroses remains a present mystery In our experience the factor is usually *hereditary* less often it is due to the particularly violent interpolation of one of the previously described exciting mechanisms (p 978) A *prolonged emotional strain* may be provocative as in returning soldiers who have suffered the anguish and anxieties of warfare it may be induced by *severe hyperthyroidism* (p 1197) *uncontrolled diabetes* (p 1246) a *nephropathy* (p 2362) or *cardiac invalidism* (p 992) Men and women of underprivileged classes appear older at thirty five or forty than most of their more fortunate associates at the ages of fifty or sixty

Clinical Manifestations —The clinical manifestations of presenile sclerosis differ from those of a generalized arteriosclerosis only in that they appear at a younger age Most often the arresting abnormality is the *hypertension* less often it is the herald appearance of a complication such as an *apoplexy* (p 1439) or a *coronary thrombosis* (p 983)

Course —The course of a presenile sclerosis is rapid and violent Those who show evidences of arterial damage before the age of thirty five rarely live to celebrate their forty fifth or fiftieth birthdays Complications are invariably encountered before this time with a fatal termination

Treatment —The treatment of a presenile sclerosis requires complete withdrawal from activities of the normal life Those with sufficient means are urged to retire and lead a sedentary existence the underprivileged are encouraged to become institutionalized wherever facilities are available Precipitating causes are eliminated if possible Attempts are made to control a *diabetes* (p 1246) iodides are given preliminary to *subtotal thyroidectomy* in individuals with *hyperthyroidism* (p 1197) operative interference is contemplated in the presence of *essential hypertension* (p 900)

Essential Hypertension

The relationship of essential hypertension to arteriosclerosis is elsewhere discussed (p 900)

Cerebral Arteriosclerosis

Cerebral arteriosclerosis may become apparent through *cerebral thromboses* or *hemorrhages* (p 1439) and *senile* or *presenile psychoses* (p 1381)

Nephrosclerosis

See *The Nephropathies* (p 2362)

Arteriosclerotic Peptic Ulcer

See *The Digestive System* (p 1763)

Arteriosclerosis of the Heart Valves

Mitral and aortic valves are particularly prone to develop arteriosclerotic change *mitral insufficiency* (p 970) is frequently encountered *aortic stenosis* (p 970) is often arteriosclerotic aortic insufficiency and mitral stenosis are more often of infectious origin

and interpolated episodes of cardiac irregularity (p 873) angina pectoris (p 890) or coronary insufficiency The electrocardiogram may show evidences of bundle branch block The left sided pattern consists of left axis deviation notching and widening of QRS depression of R T_1 elevation of R T_3 and inversion of T_1 right bundle branch block presents right axis deviation notching and widening of QRS elevation of R T_1 and depression of R T_3 An atypical right picture is that of slurring and notching of S_1 with the presence of Q_3 (ECG 36, 37, 72, 77)

Treatment —The treatment of a slow coronary closure is directed at the physiologic derangement whether it be an angina pectoris (p 890) an acute coronary insufficiency (p 895) a cardiac arrhythmia (p 873) or backward failure (p 941)

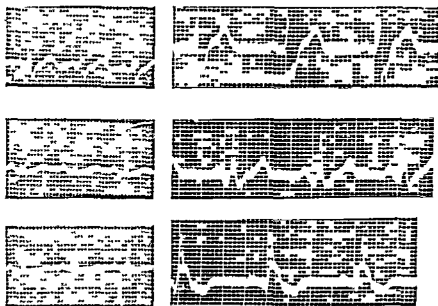


Fig 220—Standard leads on left reveal no significant changes in a male of 56 years with slight hypertension Serial cardiogram sixteen months later shows marked alterations despite absence of history of any discomfort

Those whose circulatory efficiency cannot be restored to the point where they are capable of leading useful lives are encouraged to accept their disability retire from active participation in worldly affairs and if necessary seek *the sanctuary of institutional life*

Surgery—The surgical approach to coronary closure is directed at the production of collateral circulation through the pericardial surface The technics include *cardiomyopexy* using a muscle graft *cardio omentopexy* using omentum and dusting with *talcum powder* to produce an *aseptic pericarditis* Occasionally a splendid recovery is reported by an enthusiastic proponent but results are difficult of evaluation

MYOCARDIAL INFARCTION

Myocardial infarction is the consequence of *coronary closure* (p 991) or *acute coronary insufficiency* (p 895) Its development is determined by

tial diagnosis as the leukocytosis but its delicacy makes it far more valuable

The Heart —Alterations in the cardiac sounds are of great diagnostic significance The first apical sound may become so muffled and indistinct as to be almost inaudible in a considerable number of instances there is a *presystolic gallop* which may be of greater intensity than the first heart sound the second apical and pulmonic sounds are often exaggerated

The cardiac rate is usually accelerated to 100 or 120 beats per minute disturbances of rhythm are very common and include fibrillation and flutter of the auricle premature contractions and partial or complete heart block ventricular tachycardia and Adams Stokes attacks are rare

Pericarditis —The presence of the pericardial *friction rub* which depends upon the extent of the area of myocardial infarction is noted in no more than one quarter to one third of all instances it is often transitory and may not be heard

Blood Pressure —The blood pressure response to an acute coronary closure is dependent upon the extent to which the myocardium is weakened and the degree of the accompanying shock In most instances there is a sharp fall in the *systolic* reading with less alteration in the *diastolic* level comparable changes are not seen in unmodified angina pectoris

Digestive Symptoms —Nausea vomiting abdominal pain and distention are so common in an acute coronary closure that the syndrome masqueraded for years as an *acute indigestion* The referred subjective symptoms are often associated with localized tenderness and rigidity leading to sufficient simulation of intra abdominal disease to consider *exploratory laparotomy*

Respiratory Symptoms —In an acute closure shallow respirations are observed in association with forward failure *Dyspnea* and *orthopnea* occur when the circulatory disturbance is essentially congestive *Cheyne Stokes irregularity* is not uncommon

Urinary Symptoms —In the presence of significant hypotension urinary secretion is impaired there may be *anuria* in extreme instances transitory *glycosuria* (p 3673) may be noted

Forward Circulatory Failure —In most instances the attack of acute coronary closure is associated with evidences of *forward failure* (p 920) In some individuals this may take the form of an attack of *syncope* (p 921) with masking of the precordial pain in others the syndrome of *shock* (p 928) develops immediately or later in the course of the affliction

The general appearance of the patient and his facies are more dependent upon the degree of shock than the effects of the coronary accident With significant forward circulatory failure the face is ashen and cyanotic the skin is cold and moist there may be an initial fall in temperature weakness is profound the pulse is thready small and rapid and the blood pressure level is unusually low particularly in comparison with a previous hypertensive reading Sensitivity is so impaired that the complaint of pain may be overlooked and the patient is often suspected of having suffered some other type of accident

Backward Failure —To the complicated clinical picture produced by the acute coronary closure and its attendant peripheral vascular failure may be added the manifestations of congestion Under these circumstances

the degree to which the blood supply is curtailed the extent and duration of the anoxia (p 890) and the efficiency of the collateral circulation It is predominantly a disease of the male

The infarcted area under the most favorable circumstances may recover without perceptible permanent damage under less favorable circumstances the muscle tissue becomes necrotic and is replaced by scar tissue The area of myocardial fibrosis under strain weakens with dilatation of the ventricular cavity and the production of a local aneurysm

MYOCARDIAL FIBROSIS

Myocardial fibrosis is one of the methods by which an infarcted myocardial area responds to an injury It should not be regarded as a *myocarditis* which implies an inflammatory reaction nor should it be called a *myocardosis whose implication is vague and uncertain*

ANEURYSM OF THE VENTRICLE

The aneurysm of the ventricle is the final local change following the development of *myomalacia* The ventricular cavity enlarges an *onion skin* intramural thrombus is laid down cardiac efficiency is markedly impaired backward failure (p 941) is inevitable a coronary artery occlusion may occur the wall of the ventricle may rupture causing sudden death a portion of the thrombus may become detached producing distant embolization often with a fatal issue The condition is inaccessible to therapeutic endeavors

ARTERIOSCLEROSIS OF THE AORTA

The arteriosclerotic process may involve the aorta in its thoracic or abdominal portions With involvement of the root there is accompanying atheromatous change in the coronary vessels (p 983) and the aortic valve becomes insufficient or stenosed (p 970)

Diagnosis—The aortitis of arteriosclerotic disease does not dominate the clinical picture as does the syphilitic variety (p 1025) it is just one more manifestation of the circulatory disturbance and rarely adds significant clinical features

Dilatation of the Aorta—The arteriosclerotic aorta eventually dilates as is demonstrable by fluoroscopy or roentgenograms Particularly in hypertensive disease (p 796) the aortic knob is seen with undue prominence to the left of the sternum in the oblique position the increase in the anteroposterior diameter is readily apparent At a later stage an aneurysmal dilatation of the thoracic aorta may occur but *saccular aneurysms* in this location are syphilitic (p 1025) almost without exception

Aneurysm of the Abdominal Aorta—Arteriosclerotic aneurysms may occur in the abdominal aorta They rarely give symptoms unless dissection occurs

The Dissecting Aneurysm—The dissecting aneurysm is caused by a rupture of the intima of the aorta Blood escapes between the coats of the aorta producing a complicated clinical picture

The rupture of the aortic intima is associated with *agonizing pain* localized to the site of the lesion The accident is accompanied by evidences of *severe shock* (p 933) though the blood pressure tends to remain ele

men were overweight and a history of vigorous effort preceding the fatal episode was obtained in 50 per cent The basis of each fatality was arteriosclerosis plaques were found in 84 per cent thrombi in 36 per cent old scars in 59 per cent and recent infarcts in 19 per cent none had evidences of cardiac hypertrophy (French and Dock J.A.M.A 124 1233 1944)

Clinical Manifestations—An acute coronary occlusion may occur as an initial manifestation of a circulatory disorder it may arise in the course of previously recognized cardiac disease Illustrative of the latter are the episodes that punctuate essential or symptomatic hypertension (p 900), valvular diseases of the heart (p 970) generalized arteriosclerosis (p 981), previous attacks of angina pectoris (p 890) or cardiac arrhythmias (p 873)

Prodromes—Preceding the attack of coronary occlusion particularly in the patient with previous circulatory disease there is often a period of days or even weeks of premonitory signs The attacks of *angina* may come more frequently and result from less effort there may be an increase in *breathlessness there may be precordial oppression or actual pain which* does not disappear when the tablet of nitroglycerin is taken the character of the anginal pain may vary in its quality or location and the patient may have an increasing sense of *impending difficulty*

Pain—Although the pain of an acute coronary closure is most often agonizing there is increasing recognition of the fact that it may be moderate minimum or even absent under certain circumstances

Characteristically coronary pain is *substernal precordial* or limited to the *upper epigastrium* the latter localization is responsible for the misleading term of acute indigestion Less typically the pain is noted in the *shoulder* the *arm* the *neck* the *jaw* or the *hypochondrium* in the last instance there may be sufficient simulation of intra abdominal disease to give rise to indications for exploratory laparotomy

The character of the pain is variable it may be agonizing or merely a discomfort it is described as oppressive' crushing squeezing or lancinating There may be strict localization or *radiation* to the upper shoulder and arm to the abdomen or into the back

See *Differential Diagnosis of Precordial Pain* (p 892)

The *duration* of the pain has no constancy it may last for a few minutes to several days but it is characterized by the fact that it is not relieved by nitroglycerin

The pain is often associated with cutaneous sensitivity it may be possible to delineate a band of *hyperalgesia* (Head zone)

Fever—Unlike the attack of angina pectoris acute coronary occlusion is usually associated with an elevation of temperature the rise may be inconsequential amounting to only a few tenths of a degree or the temperature may approximate 102° F or more

Leukocytosis—The presence of a leukocytosis in excess of 10 000 and often approximating 20 000 cells is of great differential diagnostic importance This alteration in the hemogram does not occur in angina pectoris or an uncomplicated acute coronary insufficiency (p 895)

Increase of Sedimentation Rate—Increased sedimentation of the erythrocytes precedes the leukocytosis and persists long after the white count has returned to normal The test (p 3707) has the same value in differen

vated *Fever* and *leukocytosis* are noted together with evidences of arterial obstruction in the legs Eventually, the aneurysm ruptures into a free cavity and sudden death ensues

The diagnosis of the dissecting aneurysm has only academic importance Therapeutic endeavors are without avail

Pulmonary Arteriosclerosis

Pulmonary arteriosclerosis may be primary or secondary It is caused by or associated with *hypertension of the lesser circulation* (p 919)

Acute Occlusion of the Mesenteric Arteries

The syndrome of mesenteric thrombosis may complicate an arteriosclerosis of the abdominal vessels

Clinical Manifestations —Mesenteric thrombosis is suspected when the arteriosclerotic develops sudden agonizing *abdominal pain* (p 1748) associated with *nausea* and *vomiting* Evidences of peritoneal irritation accompany the subjective distress as the result of infarction of the bowel The abdomen is tender and rigid distention is marked constipation is obstinate but bloody intestinal content may be recovered by enema Often blood pressure and temperature levels fall and the patient is observed to be in *profound shock* (p 928)

Table 65 —The Differential Diagnosis of Aortic Lesions

	Arteriosclerosis	Syphilitic Aortitis
Involvement of Thoracic Aorta	Present	Present
Dilatation of Thoracic Aorta	Present	Present
Saccular Aneurysm of Thoracic Aorta	Absent	Present
Aortic Insufficiency	Present	Present
Aortic Stenosis	Present	Absent
Coronary Involvement	Usually left	Usually right
Abdominal Involvement	Present	Absent
Serology	Negative	Usually positive

Treatment —Without surgical interference the patient with mesenteric thrombosis inevitably develops gangrene of the bowel with a fatal peritonitis (p 1923) Despite the extreme risks a laparotomy is mandatory as a life saving measure an attempt is made to resect the affected portion of the gut

Arteriosclerotic Peripheral Vascular Disease

Significant arteriosclerotic involvement of the peripheral vessels is unusual in patients below the age of fifty

Pathology —The lesions of arteriosclerotic peripheral vascular disease are usually characterized by their lack of uniformity Different portions of

prognosis cannot be estimated from the degree or duration of electrocardiographic changes

See *Differential Diagnosis of Precordial Pain* (p 892)

Treatment

The management of an acute coronary closure constitutes a provocative challenge to the capacity and ingenuity of the attending physician To meet the requirements of the exigency it is necessary to make observations with a minimum of disturbance to the patient to project what is happening in terms of physiology to avoid the superimposition of further pathologic or physiologic damage and to render positive aid by the choice of the appropriate therapeutic endeavors

Transportation—The patient with a coronary occlusion is not moved if arrangements can be made for care wherever he is stricken If transportation is required professional *ambulance service* is essential for minimum disturbance the physician accompanies his patient and must be prepared to administer the emergency treatment later described

Nursing Care—Professional nursing care is urgently requested even if it is necessary for the family to make significant economic sacrifices

Relief of Myocardial Anoxia (Oxygen Therapy)—The suspicion of the presence of an acute coronary closure is sufficient indication for the immediate institution of oxygen therapy It is a grave error to await the appearance of the more urgent demands of anginal pain cyanosis dyspnea or restlessness The practitioner whose vision encompasses the nature of the physiological disturbances plans his therapy with a view to preventing or at least diminishing the extent and degree of myocardial infarction he does not wait for the appearance of gross evidences of forward or backward circulatory failure before administering oxygen (p 3827)

Analgesia—While the oxygen apparatus is being obtained and assembled intravenous injection of *opiate* preferably 2 mg (1/32 gr) of dilaudid (p 3854) is administered for rapid relief of pain and to allay restlessness Repetition of the dose depends on the reaction of the patient Another injection is required if the symptoms persist If there is accompanying emesis the suspicion of *morphine vomiting* requires substitution of a barbiturate (p 3839)

Restoration of Sinus Rhythm—The frequency with which cardiac arrhythmia occurs in the first days following an acute coronary closure has led to the excessive use of oral doses of *quinidine sulfate* (p 861) Despite our strong advocacy of this drug when indicated we do not favor its administration in an acute coronary closure unless the arrhythmia is causing obvious embarrassment of the circulation

When quinidine is administered after the initial probatory dose of 0 2 gm (3 grains) large doses are required (0 3 to 0 6 gm [5 to 10 grains]) at one or two hour intervals if the need is great

Treatment of Forward Failure—The treatment of the shock that accompanies an acute coronary closure presents many difficult problems Each method that has promise of alleviating the forward failure holds a definite threat to other existent physiologic derangements Thus the *bandaging* of three extremities requires a good deal more movement of the patient than is wise under the existing circumstances the injection of

an involved extremity may be affected to different degrees the arms rarely if ever participate in the process There is no associated phlebitis but the intimal roughening predisposes to the development of thrombus formation (p 1123)

Clinical Manifestations—The clinical manifestations of significant arteriosclerotic disease of the peripheral vessels are usually of minor importance unless a complication develops in the nature of a major arterial occlusion The patient complains of *coldness weakness* and irregular *pain* in the legs *Intermittent claudication* is frequently noted with severe cramps in the calves after walking a short distance the latter are characteristically relieved by rest and recur upon exertion much in the manner of an angina (p 890) In all likelihood the phenomenon like angina is due to a local anoxia of the musculature

Nocturnal cramps in the calves or toes with dorsiflexion of the toes may be a principal complaint arousing the patient from sleep The degree of the discomfort is extreme relief is often afforded by vigorous rubbing or forced ventriflexion of the involved toes

Local examination often clarifies the diagnosis The skin is dry thin and cold *trophic disturbances* are seen in the nature of thickening and ridging of the nails The peripheral pulses are variable in the anterior and posterior tibial regions the *oscillometric readings* are unequal or bilaterally depressed Dependency of the legs is associated with an unhealthy cyanotic discoloration

Complications—The principal complication of arteriosclerotic disease of the peripheral vessels is a gangrene due to a thrombotic occlusion of a large vessel Slow closures are usually compensated by the development of an effective collateral circulation They rarely produce clinical phenomena

Vascular Thrombosis—With a sudden occlusion of a large vessel the patient experiences localized *pain* of great severity the foot turns pale but later develops a blue and then a purple color the skin is cold the peripheral pulse cannot be palpated

Gangrene—In those instances in which an effective collateral circulation is not promptly established greater or lesser areas of the toe or foot undergo gangrenous change The involved area may be a small zone parallel to the toenail on the great toe it may start in a callus or a corn and it may involve one or more of the toes the foot or the entire leg

The gangrenous lesion develops slowly At first the area appears purple later it turns black developing a border about which the skin becomes erythematous and slightly puffy Without surgical intervention there may be spontaneous amputation of the part Lesions in which the gangrenous process is moist are usually much more extensive than the dry variety

Diagnosis—The differential diagnosis of vascular diseases of the extremities is tabulated in Table 66

Treatment—The disabling symptoms of peripheral vascular disease are the expression of deficient tissue oxygenation anoxic tissue is partially devitalized and is abnormally susceptible to trauma and infection The aims of treatment embrace the protection of the tissues methods to increase the blood flow and the alleviation of pain

the patient is *dyspneic* there is a constant *cough* *moist rales* are audible at the pulmonary bases the *liver* is enlarged and tender and the *peripheral veins* may be engorged and congested

The infrequent occurrence of backward failure in an acute coronary closure is due to the simultaneous presence of forward failure (p 920) which tends to prevent congestion by the diminution of venous return to the auricles

Fluoroscopy—Though the procedure is not advocated the diagnosis of an acute coronary closure leading to myocardial infarction can be made by fluoroscopic observation of the cardiac shadow During the ventricular contraction the infarcted region *bulges* or shows little or no motion in contrast to *systolic retraction* of the remainder of the heart muscle (p 796)

Electrocardiography—Myocardial infarction may produce a wide variety of changes in the electrocardiogram (**ECG 6, 7, 8, 9, 10**) The classic patterns of an acute coronary closure include the following

1 Q waves appear in certain leads Q_1 and Q_4 are seen in anterior wall infarctions Q_2 and Q_3 in posterior wall closure
2 The amplitude of the R wave may diminish in certain lesions producing the characteristic low amplitude QRS complexes
3 The R S T segments may be displaced they are elevated in Leads 1 and 4 in anterior wall infarction and in Leads 2 and 3 in posterior closure Reciprocal depressions are observed in the other R T segments
4 The T waves may become inverted in the leads which show elevation of the R S T segment (the coronary T wave) Thus T_1 and T_4 may become inverted in anterior infarction and T_2 and T_3 in posterior wall infarction
5 The mirror image of T_1 is identical with T_3
6 Conduction defects develop in the absence of digitalization
7 In an anterior wall infarction the changes are similar in Leads 1 and 2 and reciprocal in Lead 3
8 In posterior infarction the changes are similar in Leads 2 and 3 and reciprocal in Lead 1

Maximum information is obtained from serial tracings The 'small signs' are definitively apparent if a tracing has been taken before the closure The manifestations produced by digitalis (p 854) must be discounted before interpretation

Course—There is no characteristic clinical course in an acute coronary occlusion, the patient may die instantly or he may ignore the incident the sequence of events being recognized only at a later time when the history is recounted and an electrocardiographic tracing depicts characteristic changes Most often the course of the disease is that of an acute illness lasting several weeks to several months The factors which determine the course include the extent of the area of myocardial infarction the adequacy of the anastomotic channels the degree of peripheral circulatory failure the character and duration of the cardiac arrhythmia and last but far from least the intelligence with which the condition is managed The

TABLE 66—DIFFERENTIAL DIAGNOSIS OF PERIPHERAL VASCULAR DISEASE

	Arteriosclerosis	Thrombo angiitis	Raynaud's Disease	Acrocyanosis	Erythromelalgia
Sex	Male	Male	Female	Female	Either sex
Age	Over 50	Under 50	Under 50	Any age	Any age
Predisposing Cause	?	Tobacco epidermophytosis	Cold	Cold	Warmth
Leg Involvement	Universal	Universal	Not always	Present	Universal
Arm Involvement	Rare	Common	Usual	Present	Unusual
Coronary Involvement	Frequent	Frequent	Absent	Absent	Absent
Phlebitis	Rare	Frequent	Absent	Absent	Absent
Claudication	Present	Present	Absent	Absent	Absent
Pain	Mild to moderate	Severe intractable	Mild	Mild	Mild
Color Changes	Constantly present	Constantly present	Attacks of pallor and cyanosis	Attacks of cyanotic mottling	Attacks of redness
Trophic Changes	Present	Severe	Sclerodactyly	Hyperidrosis	Hyperidrosis
Oscillometer	Diminished	Diminished	Normal	Normal	Normal
Reactive Hyperemia	Poor	Poor	Good	Good	Normal
Pulses	Irregular faint	Obliterated	Normal	Normal	Normal
Vessel Wall	Thick	Thick	Normal	Normal	Normal
Prognosis	Poor	Poor	Excellent	Excellent	Excellent
Angiography	Occlusion	Occlusion	Normal	Normal	Normal
Sympathectomy	Rarely useful	Useless	Great relief	Not required	Not required
Muscle Atrophy	Present	Marked	Absent	Absent	Absent

Diabetics—The complication of acute coronary closure in the diabetic is of serious moment since the deranged physiologic processes favor the precipitation of *acidosis* (p 721) Optimum management calls for liberal doses of *insulin* covered by an adequate intake of *carbohydrate* to prevent *hypoglycemia* (p 733) At least 1 gm of dextrose is administered for each unit of insulin a solution of 50 per cent of the sugar may be given by vein while the insulin is administered subcutaneously An effort is made to prevent hypoglycemia and acidosis this is best accomplished when the urine contains glucose but no acetone bodies (p 1252)

Drugs to be Avoided—The patient who suffers from an acute coronary closure may be in greater jeopardy from overtreatment than neglect Among the commonly used pharmacological agents whose introduction we oppose with greatest vigor are *caffeine camphor nitroglycerin strychnine coramine* the *digitalis substitutes and derivatives metrazol alpha lobeline* preparations of the *calcium salts prostigmine* and *posterior lobe pituitary extracts*

Summary—The management of the acute phase of the coronary closure may be summarized as follows

Mandatory Measures

1 Immobilization
2 Nursing care
3 Oxygen inhalation
4 Analgesia with intravenous opiate or sedation with intravenous barbiturate

Optional Measures on Indication

1 For immediate treatment of marked shock hypodermic of 0.5 to 1 cc of 1 per cent neosynephrin or 1 1000 epinephrine
2 For intense backward failure digitalization with intravenous digoxin 0 25 mg in 10 cc of saline by slow injection
3 For Cheyne Stokes breathing intravenous injection of 0 5 gm aminophylline in 10 cc of saline by slow injection
4 For continued or progressive forward failure bandage three extremities or infuse 250 cc of plasma
5 For continued or progressive backward failure 1 or 2 cc of mercurial diuretic by intramuscular injection
6 With progressive or repeated closure and threatened or actual embolization anti coagulant therapy with oral dicoumarol or subcutaneous deposits of 200 mg of heparin (p 1050)
7 With intractable irregularity oral doses of quinidine sulfate 0 3 to 0 6 gm every 1 or 2 hours

After Treatment—The problems that confront the practitioner do not dissipate with the survival by the patient of the initial insult The days and weeks which follow bring up many difficult problems which require thoughtful consideration in the effort to return the patient to his pristine usefulness

Quinidine and Digitalis—When circulatory equilibrium has been re established the physician reconsiders the wisdom of prescribing *quinidine* or *digitalis* The former is advised if irregularities persist the latter is

Protection of Tissues—The poorly oxygenated extremity must be protected from trauma and cold Injury may be inflicted accidentally by the activities of daily life or by overzealous medical attention applied by patient or physician The patient s occupation should be such that knocks and bruises are avoided

CARE OF THE FEET—Since the lower extremities are most often involved the hygiene of the feet is especially important Adequate foot covering is essential shoes should not rub the feet and the leather over the toes should be fairly loose with at least one half inch between toe and shoe tip socks should preferably be of soft white wool which cushions the feet and maintains temperature circular garters are forbidden and the patient is warned to avoid crossing his legs

The skin is kept well lubricated to prevent fissuring and secondary infection The feet are washed in soapy water every other day they are patted but not rubbed dry and if the skin tends to be dry they are anointed with olive oil or lanolin Sweaty feet are well powdered with talcum before donning the socks

PREVENTION OF GANGRENE—Of greatest importance in the prevention of ulceration and gangrene is the treatment of *dermatophytosis corns* and *calluses* In the presence of devitalized skin it is usually dangerous to use *strong salicylic acid preparations* (p 3126) especially in the treatment of dermatophytosis Far better are soaks of dilute potassium permanganate (1 6000) applied for five to ten minutes daily for a week or two A proper strength is obtained by dissolving a 2 grain (120 mg) tablet in a quart of water The treatment course may be repeated as necessary

Corns and calluses must be treated only by the expert They are sand papered gently after a preliminary soak in water Under no circumstances should the commercial corn or callus removers be used since they predispose to ulceration and gangrene Ingrown toenails are prevented by cutting the nails off square rather than rounding the edges If there is a tendency for the nail to grow into the paronychial tissue a small bit of cotton is inserted between the nail and nail bed

WARMTH—At night and in winter the problem of cold is serious since the ischemic extremity is unable to accommodate to low temperature by vasodilatation and increased blood flow Body heat is conserved by woolen socks and extra blankets if the coverings are annoying to the patient a cradle is placed in the bed A turned pillow beneath the soles of the feet keeps covers from pressing upon the feet

EXTERNAL HEAT—In threatened gangrene external heat is required An attempt is made to maintain a level of 40 C under the covers This may be accomplished by means of an electric pad or blanket turned on to low speed hot water bottles are dangerous If possible a thermostat may be obtained for attachment to a cradle containing electric bulbs

REFLEX HYPEREMIA—Reflex hyperemia of the extremities may be induced by immersing the extremities in a water bath at 44° C for one half hour Warm baths are advocated if the patient is not in great pain

REFRIGERATION—Refrigeration of the extremities has been used for intractable pain and to reduce local metabolism in threatened gangrene

TOBACCO—Tobacco has a definitely deleterious effect on the patient with peripheral vascular disease Its vasoconstrictor effect has been proved

an effectual dose of epinephrine (p 3877) diminishes venous return to the heart favors the further development of myocardial anoxia (p 890) and may initiate a cardiac arrhythmia to produce a far more desperate situation than was previously present, and an infusion of *plasma* by increasing the total blood volume may provoke an acute congestive failure (p 941)

Despite these hazards a sufficiently profound degree of shock so that the systolic blood pressure falls to a level lower than 70 mm of Hg may result in death within a very short time The practitioner under these circumstances is forced to institute active therapy In this treacherous situation, with courage in hand he may consider the subcutaneous injection of 0.5 to 1 0 cc of 1 per cent *neosynephrin* the oral use of *sodium lactate* (p 938) a slow intravenous injection of 50 per cent *dextrose* or a drip infusion of *plasma* or *citrated blood*

Digitalization—Every effort should be made to avoid the use of digitalis within the first few days or weeks following an acute coronary closure For reasons elsewhere detailed (p 894) it is impossible for the clinician to predicate whether the medication is conducive of good or evil Experiences show that no great beneficial result is to be anticipated yet on the contrary detrimental effects may be observed due to the increased sensitivity of the anoxic myocardial area and to increased hazard of embolization

In instances of backward failure with intense pulmonary and hepatic engorgement the use of the drug may be initiated in a probatory fashion Even then however it is far safer to attempt to remedy the situation by the use of diuretics as next described

Mercurial Diuretics—Following an acute coronary closure and recovery from the associated manifestations of forward failure the presence of congestive symptoms may warrant consideration of an intramuscular injection of a *mercurial diuretic* a probatory dose of 1 cc is administered intravenous injections are avoided lest they produce serious immediate reactions the larger intramuscular dose of 2 cc is reserved for those patients who fail to respond to the smaller amount The efficacy of the mercurial may be enhanced by the oral use of ammonium chloride 4 to 6 gm (60 to 90 grains) daily or an intravenous injection of decholin if the situation is urgent

Anticoagulants—The uses of dicoumarol orally or heparin by subfascial deposit (p 1150) hold great promise for active therapy in the hands of those experienced in the use of the anti-coagulants

Aminophylline—Despite the widespread and enthusiastic use of aminophylline we are opposed to its administration except in the presence of Cheyne Stokes respiration Under these circumstances it may be given in intravenous doses of 0.3 to 0.5 gm (5 to 7½ grains) diluted in at least 10 to 20 cc of fluid Needless to say, a very slow rate of introduction is advised

Nitrites—The use of the nitrites is avoided as soon as it is definitely established that the patient is suffering from an acute coronary closure with myocardial infarction The drug will not relieve the pain as it does in an angina It may increase the intensity of the physiologic derangement it favors the production of shock diminishes the venous return to the heart and adds to the element of myocardial anoxia

by numerous plethysmographic studies following the use of standard cigarettes and the so called denicotinized tobacco products The complete prohibition of tobacco in the presence of significant peripheral vascular disease is a positive therapeutic order (p 3884)

Postural Exercises—Postural exercises are useful in efforts to maintain and increase the local blood supply *Buerger's exercises* are based on the following principle When the limbs are in a dependent position, blood flow is increased because of increase in hydrostatic pressure in vascular insufficiency the dependent limb must be raised to empty its blood and obtain a fresh supply The best effects are obtained by allowing the limb to fill completely to the point of most marked erythema the extremity is then elevated until it becomes blanched after which the procedure is repeated

In practice the patient lies on his back and elevates his legs or arms for the predetermined filling time usually not more than two minutes The legs may be supported by a chair laid upon the bed face down with its back covered with pillows At the end of the blanching period the patient sits up and lets his feet hang over the side of the bed until maximal filling has occurred as evidenced by the intense redness of the skin This usually takes three minutes after which the supine position is resumed for two minutes the legs being kept flat

It is recommended that the exercises be repeated for periods of thirty minutes several times a day Usually five to six complete cycles may be run through at each period For those who are too weak an *oscillating bed* is available which carries through the motions automatically

The exercises should not be done in the presence of gangrene or infection

Drugs—Alcohol (p 3847) papaverine (p 3859) and demerol (p 3863) are useful drugs for the relief of peripheral vasospasm *Alcohol* is given in the form of whiskey *in an amount sufficient to provide about 0.5 cc* per kilo (0 25 cc per pound) of body weight. The effects on the vessels last for about four hours and the drink may be repeated several times during the day

Papaverine is given by mouth under ordinary circumstances in a dose of 22 to 44 mg (⅓ to ⅔ grain) every four hours If there is collateral *arterial spasm and embolism the drug is injected intravenously* in doses of 0 065 to 0 13 gm (1 to 2 grains) with a repetition in three hours

Demerol may be given orally in a dose of 25 to 50 mg (⅜₁₂ to ⅚ grain) every three or four hours The subcutaneous dose is 50 to 100 mg (⅚ to 1 ⅔ grains) in instances of severe pain

NOT RECOMMENDED—Among the preparations which have enthusiastic advocation but no consistently beneficial effects in the treatment of these disorders are *mecholyl* (acetyl beta methylcholine) *doryl* (carbaminoyl choline) the *nitrites* the *xanthines* particularly aminophylline *and* the various *tissue extracts* such as *insulin free pancreatic extract* and the like

Sympathectomy—Lumbar sympathectomy is of considerable value in vasospastic disorders that are not accompanied by organic arterial change (p 996) The operative procedure has *little place in the management of* arteriosclerotic peripheral vascular disease

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occlusion the patient requires institutionalization and surgical consultation Non-operative therapy consists of the production of a *procaine block* to relieve spasm and obtain adequate nutrition for the salvaging of the peripheral tissue If this measure is unsuccessful embolectomy is considered The use of anticoagulants especially *heparin* (p 1050) gives great promise but there are occasions when *amputation* must be performed preferably by the refrigeration technic The latter greatly diminishes the suffering of the patient and all but eradicates the factor of shock (p 928) Following amputation and the healing of the stump the patient is fitted with an adequate support or an artificial limb

PHLEBOSCLEROSIS

Phlebosclerosis is a process of only minor importance Occasionally the condition is noted peripherally in ancient varicosities (*vein stones*) at times pelvic calcified vessels cast misleading shadows in roentgenograms taken for observation of the lower urinary tracts

Phlebosclerosis *requires no therapy*

ordered in the presence of continued manifestations of *backward failure* (p 941)

Diet—For the first few days no attention need be paid to fluid intake or nutritive demands If the patient complains of thirst he may be given *spoonful doses of water If this is accomplished* without incident, larger amounts are offered, and later clear broth or tea may be substituted by way of variety With further favorable progression small amounts of nutrition are offered at irregular intervals depending upon existing circumstances The patient may be fed one and then two tablespoonfuls of gruel thick soup mashed potato custard or milk toast he may take one then two to four ounces of warm milk through a drinking tube, later a soft boiled egg is offered and sips of orange juice or very weak coffee

Gradually if all goes well the dietary intake becomes a little more orderly An attempt is made to give frequent small soft meals whose caloric value does not exceed 1200 daily and whose fluid intake is such that approximately 1200 cc of urine are voided each day

Oxygen—Oxygen inhalations are continued constantly until pain fever and leukocytosis have abated Thereafter they are given at ten minute intervals every one, two or four hours they are resumed immediately on the appearance of precordial distress breathlessness or change in color

Sedation—For at least the first week or ten days liberal doses of sedatives are given during the day and a double dose of a hypnotic at bedtime We advocate the use of 32 mg (½ grain) of *phenobarbital* (p 3839) at three or four hour intervals from breakfast time until the evening meal we prescribe 0 2 gm (3 grains) of such preparations as *sodium seconal* upon retiring The *opiate preparations* (p 3853) are reserved for the appearance of actual pain restlessness or anxiety

The Bowels—For the first few days no attention need be paid to the bowels unless the patient complains of abdominal distress or there is obvious distention When it becomes necessary to evacuate the intestinal tract the simplest measures are employed A glycerin suppository is inserted and the patient is instructed to evacuate into paper or old rags if the effort of raising on a bed pan seems excessive A retention enema of 1 to 2 ounces of oil is instilled if the suppository alone proves ineffectual These efforts failing the patient is turned on the side and a small and gentle irrigation is attempted one half to 1 ounce of mineral oil may be given orally the night before an anticipated irrigation Finally if necessary the patient is lifted by two persons placed on a warmed bed pan and given a gentle rectal flush under the direct supervision of the practitioner

Convalescence—With the onset of convalescence the practitioner becomes less of a physiologist and pharmacologist and more of a *psychotherapist* He is required to curb the mental and physical activities of his patient without producing a state of alarm that may result in a serious emotional disturbance he must inculcate a spirit of optimism without being so cheery as to leave his patient with the impression that the danger has passed and smooth sailing is ahead he must be staid but not somber lest he superimpose an anxiety neurosis and a cardiophobia (p 1347) on the already sufficient difficulties

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Treatment of Arterial Occlusion—With the onset of an acute arterial

Activity—At some time between the tenth day and the third week the patient is given gentle *massage* to the limbs later *passive motion* (p 3756) is inaugurated and muscular activity by movements of the legs and arms is initiated Prolongation of immobility offers definite hazard in the nature of peripheral phlebothrombosis with embolizations (p 4122)

Sometime between the third and sixth weeks providing that the acute symptoms have subsided for a period of at least ten days the patient may cautiously sit by the side of the bed with feet supported on a chair This first excursion is made in the presence of the physician who notes the general effect and any change in the pulse rate

If all is well the patient may stand momentarily on his feet while a chair is rolled up next to the bedside The periods of sitting up are increased the chair is moved away from the bed step by step until the patient is enabled to make his way to the lavatory here he indulges in the indescribable pleasure of once again sitting on a toilet seat for the evacuation of his bowels

By cautious and graded stages the convalescent is given the privilege of the range of his own room later the rest of the house becomes his beat finally he is ready for an excursion into the open air on a fine day when the sun is shining

Complications—During the course of the illness the equanimity of the sick room may be rudely interrupted by the appearance of some complication At any time between the third and tenth days following an acute episode fragments of the thrombus may break off enter the peripheral blood stream and produce *embolization in the brain the viscera or* the extremities a fresh area of *closure* with recurrent symptoms may be encountered with progressive weakening of the ventricle wall and the development of an aneurysmal dilatation evidences of *backward failure* (p 941) are added to preexistent difficulties a *cardiac arrhythmia* (p 873) may be inaugurated with disastrous effects upon circulatory efficiency

Treatment—The treatment of complications is symptomatic cardiac tamponade from effusion may call for paracentesis of the sac (p 852) an arrhythmia requires the use of quinidine (p 861) progressive backward failure demands digitalization (p 859) a recurrent coronary thrombus calls for reinstitution of the original regimen

With embolization anti coagulant therapy merits consideration with oral dicoumarol or injections of heparin (p 1050) a peripheral embolus in or beyond the iliacs may be removed by embolectomy if paravertebral block fails to result in adequate circulation to the periphery

SLOW CORONARY CLOSURE

The slow coronary closure may be of incredible extent and yet remain asymptomatic Under these circumstances the vascular lesion is diagnosed by the electrocardiographic tracing or it may be noted as an unexpected finding at autopsy

Clinical Manifestations—Most often the course of a slow coronary closure is punctuated by recurrent attacks of acute coronary thrombosis giving rise to the clinical symptoms previously described (p 984) In the remainder of the afflicted the patient shows evidences of progressive circulatory deficiency (p 920) diminished responses to therapeutic endeavors

pulse but a local force in the vessel itself Allen and Brown advanced the hypothesis that the disease is ordinarily an equivalent of a *psychoneurosis* or *neurasthenia* and Bernheim and London suggested that an *inadequate calcium intake* may be associated with heightened irritability of the digital vessels as expressed by sensitivity to cold

Pathology.—*In the early stages there are no pathologic evidences of* Raynaud's disease In the advanced instance the arteries show intimal thickening atrophy and fibrosis of the media and a perivascular cellular *infiltration The corium is fibrotic with atrophy of the skin appendages* Decalcification and resorption occur in the bones of the terminal phalanges There is little question but that all of these lesions are of a secondary nature

Clinical Manifestations.—Raynaud's disease occurs more frequently in *females* between the ages of adolescence and middle age The specific temperature which precipitates an attack may vary from patient to patient but usually is within the narrow range of 40 to 55° F Less frequently a patient may have spasm on returning to a warm environment from the critical range of low temperature Secondary factors which modify the response include humidity the warmth of the clothing unusual fatigue the imbibing of cold or hot liquids and emotional stress and strain

The site of the vasospasm is ordinarily the extremities occasionally the tip of the *nose* and the *ear lobes* are involved the *feet* are affected much less frequently *than the upper extremities the fingers* other than the thumb are usually involved

The severity of an attack depends upon the length and degree of chilling *The local sequence of events involves the appearance of pallor cyanosis* and then *redness* During the period of blanching there is often pain a burning sensation is noted in the phase of hyperemia

Without complicating trophic changes the *normal color of the digit* usually reappears when warmth is applied Otherwise *trophic changes* occur with local ulceration of the finger or toe splintering of the nails resorption of the bone of the terminal phalanx atrophy of the skin and its appendages and sclerodactyly

Diagnosis.—The diagnosis of Raynaud's disease should offer little difficulty The appearance of the phenomenon in a female before the middle years distinguishes it from arteriosclerotic and thrombo angiitic lesions of the extremities The oscillometer readings remain normal angiography reveals no evidence of block of the vessel

See *Differential Diagnosis of Peripheral Vascular Disease* (p 996)

Idiopathic Raynaud's disease requires differentiation from the symptomatic variety In the latter the cause for the disturbance is the prolonged use of *crutches* irritation of the *brachial plexus* or the presence of the *scalenus anticus syndrome* (p 2953) The last disease is invariably unilateral brachial plexus irritations are accompanied by demonstrable motor and sensory accompaniments crutch lesions are distinguished by the history

Treatment.—The patient with Raynaud's disease may suffer only mild incapacitation which abates with the passage of years Under these circumstances little *is required other than protection from cold* In those patients in whom a low basal metabolic rate is demonstrable the administration of

structure of the antigen and is modified by alterations in chemical composition The specificity of certain antigens is determined by *haptenes* which are non protein prosthetic groups These are capable of reacting with the antibodies called forth by the complete antigen but cannot elicit them The relationship of haptenes to antigenicity is well illustrated by the different polysaccharides present in the capsules of type specific pneumococci (p 200)

The substances commonly used as antigens in the development of active immunity include *killed organisms* (bacteria rickettsiae and viruses) *live attenuated organisms* (bacteria rickettsiae and viruses) or *bacterial products* Preparations of living or killed organisms are *vaccines* those in which bacterial products are used are *toxins* or *toxoids* Inactivation of living organisms by ultraviolet irradiation promises to provide a means of potent immunization especially with virus vaccines

Vaccines Composed of Killed Bacteria —Suspensions of killed bacteria in normal saline constitute the largest group of vaccines *Stock vaccines* are prepared from virulent laboratory strains *autogenous vaccines* are prepared from organisms isolated from a particular patient and used in the treatment of this patient

Stock vaccines are widely used as immunizing agents The organisms should be antigenically identical with those strains isolated from clinical cases and all the common specific antigenic types of a *polyvalent organism* should be represented The method of killing the organism by heat irradiation or chemicals must not alter the immunizing powers

Toxins and Toxoids —Under ordinary conditions of growth many bacteria elaborate powerful soluble poisons which are antigenic and generally known as *exotoxins* Some of these as in the case of the toxins elaborated by *C diphtheriae Cl tetani* and *Cl botulini* constitute the principal hazard associated with infection with these organisms Most exotoxins are proteins or are closely bound to proteins They are readily destroyed by proteolytic enzymes are heat coagulable and are precipitated by salting out processes In some instances they have been crystallized

In general exotoxins have marked specific toxicologic actions which are directly responsible for the manifestations and pathology of the disease caused by the invading organism *Diphtheria toxin* for example causes peripheral neuritis myocardial depression and adrenal cortical necrosis *tetanus toxin* on the other hand is a powerful stimulant of the central nervous system producing generalized convulsions followed by depression from exhaustion of the motor areas A constant feature of the action of these toxins is the presence of a definite latent or incubation period before the onset of their action The reason for this is obscure It may represent the time required for the toxin to enter certain cells upon which it acts

In addition to exotoxins bacteria also give rise to *endotoxins* These are degeneration products of dead organisms and differ from exotoxins in several respects They have a more complicated chemical structure and are poorly antigenic their pharmacologic actions are relatively non pecific as a rule their actions are preceded by a short latent period or none at all

Exotoxins being powerful antigens give rise to antitoxins when injected parenterally These substances combine when in contact according to the laws of multiple proportions of inorganic chemistry The union neutralizes

less permanent and is accomplished by an ability of the cells to respond quickly and efficiently to the offending agent Its great value lies in the prevention of disease its principal disadvantage is the long latent period required for the development of resistance

NATURAL IMMUNITY

Natural immunity is the resistance to infection that is normally possessed by a species or an individual under normal and natural conditions

Natural immunity is poorly understood It is observed both as a species and an individual variation Thus laboratory workers are familiar with the fact that only certain animals can be infected with certain parasites Experimental investigation of syphilis for instance is limited to chimpanzees monkeys and rabbits

Racial immunities and susceptibilities are also observed Diseases of aliens in the tropics are quite different from those of the natives Explorers *and mining engineers fall critically and often fatally ill with malarias* and the dysenteries while their less protected native workers apparently are immune perhaps because they have chronic infection or have survived previous attacks

Individual immunities are commonly observed by the practitioner not all of whose patients succumb to exanthems and contagious diseases Certain members of a household fall ill while others living under seemingly similar circumstances remain well despite repeated and massive exposure

ACQUIRED IMMUNITY

Naturally Acquired Active Immunity

In naturally acquired active immunity the patient builds up an immunity as the result of the *development of antibodies* in response to exposure to the living parasite

Relatively complete active immunity follows *smallpox scarlet fever chickenpox mumps measles pertussis typhoid fever cholera yellow fever typhus fever plague* and *poliomyelitis* By contrast there is no significant or lasting immunity conferred by an attack of gonorrhea pneumonia the common cold influenza glanders erysipelas and infections due to the pyogens

Naturally Acquired Passive Immunity

Naturally acquired passive immunity exists as the result of the *passage of antibodies from mother to offspring* through placental transmission or by way of the colostrum and milk Sufficient protective body is present in the newborn infant to defend it against the acute exanthems diphtheria and poliomyelitis for the first few months of its existence

Artificially Acquired Active Immunity

Artificial active immunization is essentially of prophylactic value It constitutes one of the great public health services

Agents Used to Produce Active Immunity—A material that is used to stimulate the production of active immunity must be *antigenic* and relatively harmless Antigenicity denotes that the substance leads to the formation of specific antibodies this specificity is determined by the chemical

CHAPTER 46

NEUROGENIC DISORDERS OF THE CIRCULATORY SYSTEM

ACROCYANOSIS

Acrocyanosis is a vasomotor disorder that involves the smaller arterioles of the skin abolition of vasoconstrictor tone results in dilatation of the peripheral vessels producing the local phenomena of the disorder

Clinical Manifestations—Acrocyanosis is more frequently seen in the *female* it may occur at any age It is more common in individuals who are hypersensitive and give other evidences of *autonomic imbalance* (p 1395) The attacks are particularly caused by prolonged exposure to *cold* they are more frequent in patients who suffer also from *arthropathies* (p 2910) and disturbances of the anterior pituitary (p 1153) or ovarian secre tions (p 2523)

The characteristic appearance in an acrocyanosis is that of an uneven mottling of a blue and red hue extending from a line above the wrists and ankles to the digits and increasing in degree distally The discoloration is intensified by cold or anxiety and relieved by the application of warmth Hypesthesia may be present The parts are habitually bathed in profuse sweat

Diagnosis—See *Differential Diagnosis of Peripheral Vascular Disease* (p 996)

Treatment—The course of an acrocyanosis is entirely benign Of itself acrocyanosis requires no treatment Alcohol injections (p 1394) of the para vertebral sympathetic ganglia are useful in the relief of the hyperidrosis (p 3460) if this symptom is of sufficient moment to warrant the procedure

RAYNAUD S DISEASE

Raynaud s disease is a vasospastic disorder that is precipitated by ex posure to *cold* The condition may be associated with *sclerodactyly* It is to be distinguished from the symptomatic entity which results from obstruc tive vascular diseases of the extremities

Etiology—The fundamental cause of Raynaud s disease has eluded defi nition Raynaud believed that the condition ought to be considered a *neurosis* characterized by enormous exaggeration of the excitomotor energy of the great part of the spinal cord Lewis concluded that the primary cause of the spasm in the digital vessels is not an abnormal nervous im

febrile increase is experienced often the patient notes an unproductive dry cough and sharply localized precordial pain (See p 892)

In some instances the onset *is misleading with severe epigastric pain* In the presence of fever and leukocytosis the resultant syndrome simulates an acute abdominal disturbance

Tuberculous Pericarditis—The fibrinous exudate of tuberculosis rarely causes a significant disturbance since the effusive element next to be described dominates the picture

Pneumococcic Pericarditis—Fibrinous pericarditis is of frequent occurrence in pneumococcus pneumonia The *friction rub is often ephemeral and* sharply localized Pneumococci are present in the exudate which is highly infectious and may progress to suppuration (p 1010)

Azotemic Pericarditis—The patient with chronic nephritis and azotemia (p 2276) often develops a terminal fibrinous pericarditis Repeated auscultation rarely fails to disclose the characteristic friction rub which constitutes an important prognostic sign indicating the onset of the preagonal stage

Myocardial Infarction—The infarcted myocardial area is often the site of an overlying aseptic fibrinous pericarditis The presence of the friction rub is of important diagnostic significance (p 3549)

Diagnosis—The diagnosis of fibrinous pericarditis is essentially a clinical discipline radiographic confirmation is absent, at most the electrocardiographic changes include an elevation of the S T segment low voltage and a diphasic or inverted T wave (p 806)

The differential diagnosis of fibrinous pericarditis requires that the underlying etiologic factor be elucidated In the absence of manifestations of rheumatic fever or a pneumococcal pneumonitis the practitioner suspects the possible aseptic causes of azotemia and coronary thrombosis If the presence of these latter conditions is not apparent through the obvious clinical features a blood chemical analysis (p 3712) and an electrocardiographic tracing should soon settle the disputed point

Course—*The course of fibrinous pericarditis is toward recovery in* the vast majority of instances Under these circumstances the rub and the accompanying constitutional manifestations disappear In the minority of patients the fibrinous process is followed by effusion (p 1008) and under these circumstances the friction rub disappears but the cardiac silhouette becomes progressively enlarged as the sac fills with fluid

Treatment—Specific treatment of fibrinous pericarditis is accomplished by the salicylates in rheumatic fever (p 186) and penicillin (p 106) in pneumococcal infections Desperation and probatory antibiotic therapy (p 114) merits trial using penicillin sulfonamides (p 88) and/or streptomycin (p 103) Symptomatic relief may be afforded by an ice cap to the precordium or by opiates

SEROUS PERICARDITIS (PERICARDIAL EFFUSION)

Serous pericarditis is essentially a progression of the fibrinous process The etiologic agencies *are most often rheumatic fever* (p 186) and the *tubercle bacillus* (p 252) rarely effusive pericarditis is the result of *pneumococcal infection* (p 199), *azotemia* (p 2276) or *coronary thrombosis* (p 983)

exists in civilian practice as a rare and minor disturbance Unfortunately fox hole warfare has produced a high incidence of this incapacitating and at times crippling disorder particularly among the infantry

Clinical Manifestations —The histories of those who suffer from trench foot are almost stereotyped The soldier reports having been in a fox hole trench or the open field so that he was unable to remove wet shoes and stockings for several days Most often the factor of cold was added as an environmental influence particularly during the night and the early hours of the morning When finally the footwear could be removed the feet were numbed and appeared dead white or a mottled white with blue Pain was noted in the feet and toes with aching of the calves Handling of the parts gave the sensation of wooden feet With removal of the shoes and stockings and warming of the feet edema developed with bleb formation so that it was impossible to replace footwear Often the soldier described hours of effort with the assistance of comrades before the shoe could again be put on In the most severe instances gangrene developed with spontaneous or surgical amputation

Few of the men so afflicted were able to return to duty In convalescence disabling burning pains are noted Short walks produce agonizing distress Sensitivity to changes in external temperature are so severe that most of the sufferers state that they sleep with feet exposed not being able even to stand the pressure and heat of blankets Cold is endured no better than heat Examination reveals color changes when the patient is seated with feet dependent The skin becomes mottled and cyanotic Quite characteristically the great toe assumes a position of drop whilst the other toes fan Sweating is so profuse that socks must be changed sometimes hourly and can be wrung out as though they had been immersed in water

Eventually those whose recovery is most delayed develop permanent defects such as clawfoot and pes cavus At times gangrene necessitates amputation

Pathogenesis —The pathogenesis of trench foot is clouded in mystery Not all of those exposed to identical conditions develop the condition There is no foundation to suspicions that important etiologic factors may be previous foot disorders psychoneuroses peripheral vascular disease excessive smoking the presence of metabolic disorders such as diabetes or malingering It is our personal opinion that trench foot is another manifestation of autonomic imbalance (p 1305) We believe that the condition is produced by injury to the end structures of the involuntary nervous system and that it is as cruel to brand sufferers from trench foot as psychoneurotics as it is to apply a similar label to those afflicted with neurocirculatory asthenia (p 897) This is not to deny that trench foot does not occur in malingerers and neurotics It is merely to affirm that the disturbance can also occur in good soldiers whose voluntary nervous system is well stabilized

Treatment.—The treatment of trench foot is most unsatisfactory *Prevention* is of major importance and may be accomplished by the use of *galoshes and other waterproof footwear which is also* capable of impeding the agility of the infantrymen

The *immediate treatment* consists of removal of all constrictions about ankles and feet prevention of weight bearing and gradual elevation of

Chronic Mediastinopericarditis—When the inflammatory process extends to the pleura diaphragm or chest wall the heart may be completely bound to relatively fixed structures In order to carry out its function it *undergoes tremendous hypertrophy Some of the largest hearts found* at autopsy occur in chronic mediastinopericarditis

Pick s Disease (Pseudocirrhosis Polyserositis)—In the final stage of constrictive pericarditis the hepatic veins are obstructed and the liver becomes congested enlarged and cirrhotic fluid accumulates in the pleural and peritoneal cavities perihepatitis and perisplenitis appear as terminal lesions (sugar coating)

Clinical Manifestations—In the majority of instances chronic adhesive pericarditis is an asymptomatic disorder In a relatively small number of individuals unusual clinical syndromes are encountered these vary with the nature of the pathologic manifestations but usually consist of intractable backward failure (p 941)

Pericardial Fixation—The physical signs of pericardial fixation are often clearly defined and confirmed by fluoroscopy The apex impulse is fixed change in position does not cause the normal lateral shift of 2 to 3 cm *frequently there is a systolic retraction at the apex with a diffuse cardiac* impulse a diastolic shock may be felt over the entire precordium a systolic retraction may be demonstrable in the eleventh posterior left interspace (*Broadbent s sign*)

At this stage fluoroscopy reveals irregularity in the outlines of the pericardial sac with a great diminution in the pulsations the heart fails to undergo its normal descent with inspiration if there are adhesions to the anterior chest wall Should calcification be present linear or undulating shadows are observed at the cardiac borders most commonly in the region of the left ventricle

During the purely constrictive phase the heart is small or normal in size blood and pulse pressures are low venous pressure is elevated and the patient may not suffer significant circulatory difficulty

Constriction of the Veins—With constriction of the veins the heart may undergo great hypertrophy provided that the pericardial encasement is not excessive the jugular veins are engorged the liver enlarges and becomes tender evidences of backward failure are initiated

Polyserositis and Pseudocirrhosis—In the final stage of constrictive pericarditis the liver becomes cirrhotic Fluid accumulates in the pleural and peritoneal cavities constituting the syndrome of polyserositis (p 1934) Often an apparent enlargement of liver and spleen occurs as the result of the development of perihepatitis and perisplenitis (sugar coating)

Treatment—A successful surgical procedure may convert the patient who suffers from chronic adhesive pericarditis from a state of invalidism *to one which approaches normality* The *simpler operation of cardiolysis* consists of the removal of the bones of the chest in the region of the heart *decortication* is especially important over the left ventricle so that the organ may contract against soft tissue rather than the more rigid bony structures

With constriction of the great veins a more difficult technic is required After removal of portions of the ribs and sternum the pericardium is explored and adhesions are freed portions of the pericardium are then removed to allow freer action of the heart

thyroid extract is advised The tendency of *smoking* to produce vasoconstriction justifies abolition of this habit

In an acute attack an intravenous injection of *papaverine* (p 3859) in a dose of 0 06 to 0 13 gm (1 to 2 grains) may have an immediate and efficacious result but ordinary vasodilator drugs are of little value

Sympathectomy—In refractory instances of Raynaud s disease especially with trophic disorders a sympathectomy is justifiable

Sympathetic ganglionectomy has promise of success only if the vessels are shown to be capable of dilatation This is tested before operation by the induction of reactive hyperemia or a paravertebral nerve block In the presence of marked organic arterial change sympathetic surgery holds little promise but a successful result can be anticipated if the temperature rises in the extremity within a short period of time after the vasodilating procedure has been instituted

Tetraethylammonium—Intramuscular or intravenous injections of 10 per cent tetraethylammonium produce blockage of autonomic ganglions The effects of slow introduction of 1 to 5 cc of the chloride or bromide salt (10 per cent) were encouraging in Raynaud s disease

ERYTHROMELALGIA (ERYTHERMALGIA)

Erythromelalgia is an idiopathic form of *paroxysmal bilateral vasodilatation* As a symptomatic complaint it may occur as a complication of *polycythemia vera* (p 1093) *peripheral arteriosclerosis* (p 994) *peripheral neuritis* and *tabes dorsalis* (p 1464)

Clinical Manifestations—Erythromelalgia is a rare condition that is characterized by intermittent attacks of *vasodilatation in both feet* There is severe burning or tickling located chiefly in the balls of the feet and the tips of the toes skin temperature is increased during the attack when the foot becomes intensely red and sweats considerably Between attacks the extremity presents no demonstrable abnormality

Erythromelalgia occurs equally in male and female without special age incidence The lower extremities are more commonly involved but the complex has also been seen in the *arms* The attacks are precipitated by exposure to warmth holding feet or hands in the dependent position and following activity

Trophic changes including ulceration and gangrene do not occur The distribution of the lesion is usually symmetrical Arterial pulsation is temporarily increased locally but no permanent changes are found

Diagnosis—See *Differential Diagnosis of Peripheral Vascular Disease* (p 996)

Treatment—The attacks usually respond to rest elevation of the extremity and the local application of cold compresses Contrast baths in the interim have some value from the standpoint of prevention

In the severe intractable instance it may be necessary to perform section or alcohol injection Sympathectomy has also been advocated

TRENCH FOOT (IMMERSION FOOT)

The problem of trench foot has attained major significance as a cause for disability and distress in World War II Undoubtedly the condition

Course—The course of pericardial effusion depends upon the etiologic factor Rheumatic effusions accumulate rapidly and respond well to the administration of salicylates they absorb completely and rarely reaccumulate or produce any chronic change Tuberculous effusions appear slowly and do not respond to salicylate they reaccumulate steadily and eventually go on to the production of chronic change as elsewhere described (p 1011)

Treatment—In rheumatic pericarditis the intensive administration of salicylates may prevent the necessity for performing paracentesis (p 852) Upon the development of the manifestations of cardiac tamponade (p 872) removal of the fluid is readily accomplished A preliminary injection of an opiate and careful local anesthesia are required to prevent the complication of vasovagal syncope (p 921)

SUPPURATIVE PERICARDITIS

Suppurative pericarditis is an extremely rare clinical entity Most often it results from *pneumococcal infection* in the course of a lobar pneumonia (p 2178) The pathologic process resembles the empyema observed in the pleural cavity (p 2222) In the era preceding the use of the sulfonamides suppurative pericarditis was not infrequently an unexpected autopsy finding in fatal pneumonia

Clinical Manifestations—The probable sequence of events is a fibrinous exudate with a serous effusion that becomes purulent due to the activity of the infecting organisms The diagnosis is suspected from the persistence of precordial pain the signs of effusion (p 1008) the intensity of the constitutional signs and prostration

Diagnosis—The only certain method of diagnosis is by exploratory puncture and the removal of purulent fluid

Treatment—Suppurative pericarditis is treated by intensive chemotherapy using sulfonamides (p 88) and/or penicillin (p 106) In intractable instances the cavity may be washed out with a solution of penicillin Failure to obtain a satisfactory result requires surgical intervention which may prove to be life saving

CHRONIC PERICARDITIS

The recognition of chronic pericarditis is of great importance since surgical therapy is often rewarded by an extraordinarily satisfactory result

Etiology—In the majority of instances chronic adhesive pericarditis is of *tuberculous* or *pneumococcal* origin a *rheumatic* origin is rare At times it is not possible to demonstrate the causative organism

Pathology—Various types and degrees of adhesive pericarditis are recognized, the condition may be mild and unimportant or severe and incapacitating The earliest significant lesions consist of small *synechiae* between the epicardial and pericardial surfaces and the *milk spots* of the pericardial mesothelium The process may progress until visceral and parietal surfaces are entirely adherent

Concretio Cordis—In a numerically small number of patients the pericardium is greatly thickened The adhesions become firm and calcified they constrict the hepatic veins and the cavas impeding the free flow of blood to the heart There may be an associated mediastinitis but the heart is not enlarged

CHAPTER 47

ORGANIC DISEASES OF THE CIRCULATORY SYSTEM INFLAMMATIONS AND INFECTIONS

- Acute Fibrinous Pericarditis
  - Rheumatic Pericarditis
  - Tuberculous Pericarditis
  - Pneumococcic Pericarditis
  - Azotemic Pericarditis
  - Myocardial Infarction
- Serous Pericarditis
  - Pericarditis of Rheumatic Fever
  - Pericarditis of Tuberculosis
- Suppurative Pericarditis
- Chronic Pericarditis
  - Concretio Cordis
  - Chronic Mediastinopericarditis
  - Pick's Disease (Polyserositis)
- Syphilis of the Coronary Arteries
- Nonluetic Coronary Arteritis
- Myocarditis
  - Diphtheritic Myocarditis
  - Rheumatic Myocarditis
  - Thiamine Chloride Deficiency ("Beriberi Heart")
  - Parasitic Myocarditis
  - Syphilitic Myocarditis
  - Tuberculous Myocarditis
  - Fiedler's Myocarditis
- Rheumatic Endocarditis
- Atypical Verrucous Endocarditis (Libman Sacks Disease)
- Nonbacterial Thrombotic Endocarditis
- Acute Bacterial Endocarditis
- Subacute Bacterial Endocarditis (Endocarditis Lenta)
- Syphilitic Endocarditis
- Syphilitic Aortitis and Aneurysm
- Pulmonary Arteritis
- Nonspecific Angiitis
- Visceral Angiitis
- Periarteritis Nodosa
- Thrombo angiitis Obliterans (Buerger's Disease)
- Phlebitis (p 1124)
- Lymphangitis (p 3962)
- Lymphadenitis (p 3962)
- Temporal Arteritis

The main problems involving inflammations and infections of the circulatory structures arise as the result of rheumatic syphilitic or bacterial invasions of the heart valves and the aorta In each instance the lesion is of serious consequence and presents a formidable problem for the therapist

Chronic Mediastinopericarditis—When the inflammatory process ex tends to the pleura diaphragm or chest wall the heart may be completely bound to relatively fixed structures In order to carry out its function it undergoes tremendous hypertrophy Some of the largest hearts found at autopsy occur in chronic mediastinopericarditis

Pick s Disease (Pseudocirrhosis Polyserositis) —In the final stage of constrictive pericarditis the hepatic veins are obstructed and the liver be comes congested enlarged and cirrhotic fluid accumulates in the pleural and peritoneal cavities perihepatitis and perisplenitis appear as terminal lesions (sugar coating)

Clinical Manifestations —In the majority of instances chronic adhesive pericarditis is an asymptomatic disorder In a relatively small number of individuals unusual clinical syndromes are encountered these vary with the nature of the pathologic manifestations but usually consist of intract able backward failure (p 941)

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At this stage fluoroscopy reveals irregularity in the outlines of the peri cardial sac with a great diminution in the pulsations the heart fails to undergo its normal descent with inspiration if there are adhesions to the anterior chest wall Should calcification be present linear or undulating shadows are observed at the cardiac borders most commonly in the region of the left ventricle

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Treatment —A successful surgical procedure may convert the patient who suffers from chronic adhesive pericarditis from a state of invalidism to one which approaches normality The simpler operation of *cardiolysis* consists of the removal of the bones of the chest in the region of the heart *decortication* is especially important over the left ventricle so that the organ may contract against soft tissue rather than the more rigid bony structures

With constriction of the great veins a more difficult technic is required After removal of portions of the ribs and sternum the pericardium is ex plored and adhesions are freed portions of the pericardium are then removed to allow freer action of the heart

local temperature The management of *late disability* is vexatious and discouraging As might be expected from the suggested pathogenesis of the disorder injection therapy and a surgical approach to the main ganglions and trunks of the involuntary nervous system yield nothing of value Psychotherapy in our opinion is a futile gesture and may well antagonize the good soldier who resents being labeled as a neurotic Corrective exercise is worthy of trial There seems to be no valid reason for banning smoking unless the patient wishes to avoid any possible exciting mechanism Contrast baths and sea bathing have psychotherapeutic possibilities if nothing else Massage is usually poorly tolerated but disturbances of foot mechanics require careful correction (p 3080) The return of the soldier who has suffered from trench foot to active service invites recurrence Unless the military need is great these soldiers are best marked for non combat service

SYPHILIS OF THE CORONARY ARTERIES

Coronary artery disease in the syphilitic, *is more likely to be due to* an incidental arteriosclerosis (p 983) than the specific process In the latter instance, the luetic arteritis usually accompanies an *aortitis* (p 1025), with or without *aortic insufficiency* (p 970)

Pathology —The coronary lesion of syphilis involves the mouths of the vessels more often the right and the adjacent 0 5 to 1.5 cm of the vessel wall *The combination of ostial stenosis* with insufficiency of the aortic valves constitutes a serious physiologic burden to the myocardium which usually develops great hypertrophy later the muscle fibers undergo necro sis fibrosis or myelomalacia

Clinical Manifestations —The clinical manifestations of coronary syphilis rarely develop for ten to twenty years after the acquisition of the primary lesion Their variety may be infinite there may be *paroxysms of nocturnal dyspnea* (p 942) *anginal pain* (p 890) evidence of *coronary insufficiency* (p 895) constant *substernal pain* (p 892) episodes of *cardiac asthma*

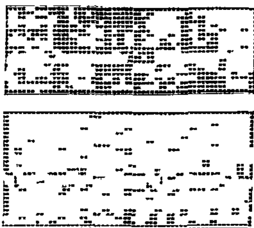


Fig 221 —*Upper* Lead I 40 year old male with thrombo-angiitis obliterans and coronary thrombosis *Lower* Lead I same patient thirteen years later showing restitution to normal

attacks of *pulmonary edema* (p 810) and sudden unexpected *death* Con gestive failure (p 941) is a late development and indicates a marked exhaus tion of cardiac reserve

Examination usually reveals widening of the supracardiac portion of the aorta accentuation of the aortic second sound or the diastolic mur mur of aortic insufficiency (p 970) The electrocardiogram gives evidences of left axis deviation The serological tests for syphilis (p 336) may be positive but often are deceptively negative

Treatment —The treatment of syphilis once vascular complications have arisen is hazardous and unsatisfactory It is doubtful whether the lesion can be benefited in any way In order to prevent the production of a Jarisch Herxheimer reaction in the root of the aorta with resultant acute closure and death a preliminary course of *iodides* (p 608) is given for several weeks thereafter a course of at least 10 000 000 units of penic illin with bismuth supplementation (p 126) offers the most hope with the least risk (p 340)

Myocardial Infarction	From coronary occlusion With precordial pain. Electrocardiographic changes leukocytosis and increased sedimentation rate (p 983)
Cerebral Hemorrhage and Thrombosis	With or without localizing motor and sensory changes (p 1439)
Backward Failure	Usually with pulmonary hypostasis (p 941)
Thrombophlebitis	With or without localizing symptoms and signs (p 1124)
Embolization	With or without localizing symptoms or signs (p 2086)
Sinus Thrombosis	Usually secondary to adjacent infection of skin, eye ear nose or accessory nasal sinuses (p 2130)
Lymphangitis and Lymphadenitis	From drainage of infected areas (p 39o2)
Acute Disseminated Lupus Erythematosus	With associated non bacterial endocarditis (p 3395)

ACUTE FIBRINOUS PERICARDITIS

Acute fibrinous pericarditis may be encountered as the result of bacterial or nonbacterial irritations of the serous lining of the cardiac sac

Etiology —Acute fibrinous pericarditis occurs as a complicating lesion in *rheumatic fever* (p 186) and *pneumococcal pneumonia* (p 2171) It is seen as a terminal event in *azotemia* (p 2276) and accompanies *myocardial infarction* resulting from coronary occlusion (p 983)

Pathology —Fibrinous pericarditis may occur in a localized area as exemplified by the myocardial infarcts it may involve the entire epicardial and pericardial surfaces as in acute rheumatic fever Under any circumstance the involved area loses the normal glistening appearance and becomes dull and opaque fibrin is deposited until in the more advanced instances the entire serous surface is covered with a shaggy exudate Small amounts of free fluid are present in the late stages the effusion overshadows the fibrinous process giving rise to the clinical picture of a hydropericardium (p 1009)

Clinical Manifestations —The characteristic physical sign of a fibrinous pericarditis is the presence of the *friction rub* that is usually best heard near the left border of the sternum the sound appears near to the surface and is increased by pressure of the stethoscope Typically it is heard in systole and diastole giving the characteristic *to and fro* quality at times only a systolic or diastolic component may be present

The pericardial friction rub is transitory it usually lasts for only a few hours but may persist for several days

During the acute process whether the underlying condition is infectious or noninfectious there are constitutional manifestations such as elevation of temperature leukocytosis and tachycardia Patients often complain of local pain and tenderness

Rheumatic Pericarditis —The fibrinous pericarditis of rheumatic fever rarely constitutes the only manifestation of the infection more often it is detected after the febrile episode has been established for several weeks At the time of the complicating pericarditis the heart rate becomes more rapid the respiratory rate increases without corresponding dyspnea a

NONLUETIC CORONARY ARTERITIS

Aside from the coronary artery disease of arteriosclerosis and that caused by syphilis significant involvement of these vessels is rarely encountered clinically In *rheumatic fever* (p 186) the lesion is overshadowed by the valvular and myocardial disturbances *mycotic aneurysms* occasionally are encountered in *subacute bacterial endocarditis* (p 1021) but these are rarely diagnosed except at autopsy

Coronary arteritis may accompany *thrombo angiitis obliterans* (p 1029) and *periarteritis nodosa* (p 1027) In each of these conditions manifestations of coronary insufficiency (p 895) coronary closure (p 983) myocardial infarction (p 992) or angina pectoris (p 890) may be accepted as a local manifestation of the more extensive arterial inflammation

MYOCARDITIS

In its present sense myocarditis is used in the narrow connotation of an inflammation of the muscle fibers of the heart Most often it is a *diffuse parenchymatous disturbance* less often it is an *interstitial infiltration* as in rheumatic fever (p 186) with its specific *Aschoff nodules* The term myocarditis should not be used for the commonest affliction of the heart muscle which is in reality a myocardial infarction or fibrosis (p 992) secondary to sclerosis of the coronary arteries (p 983)

The frequency of myocarditis is difficult of approximation since the diagnosis is rarely made during life It probably accompanies most of the acute infectious diseases and many metabolic conditions and poisonings For the most part however myocarditis does not assume clinical importance except in *diphtheria rheumatic fever thiamine deficiency trichinosis tuberculosis typhoid fever* and *syphilis*

DIPHTHERITIC MYOCARDITIS

Diphtheritic myocarditis results from the action of toxin upon heart muscle In the present era the disease and its complication have become rarities but in earlier days diphtheritic myocarditis was an insidious serious and often fatal complication

Clinical Manifestations—Most often diphtheritic myocarditis is *asymptomatic* The suspicion of the complication arises when the pulse rate increases with the advent of a systolic murmur previously absent or in the presence of a recent cardiac irregularity such as a premature contraction bradycardia or heart block The first symptom may be sudden collapse resulting in death

In patients with diphtheria of any degree of severity the possibility of myocardial involvement is ever to be feared Small circulatory signs are meticulously registered a slight increase in the pulse rate lowering of blood pressure unusual weakness restlessness or anxiety the onset of the murmur or a cardiac irregularity demand utmost precaution and diagnostic investigation by electrocardiography

Serial electrocardiographic tracings are of great comparative value changes in rhythm or the contour of the T waves suggest the diagnosis and require the practitioner to warn parent and child of the treachery of the future course

DIFFERENTIAL DIAGNOSIS OF

Fever With Circulatory Manifestations

The association of fever with manifestations in the circulatory organs has grave implications Physical examination requires supplementation with blood cultures chest x rays and electrocardiograms since the syndrome may involve bacteremia endocarditis myocarditis or pericarditis alone or in combination

CAUSE	DIAGNOSTIC FEATURES
Staphylococcus	May cause bacteremia and endocarditis. Get blood culture (p 151)
Streptococcus	May cause bacteremia and endocarditis. Get blood culture (p 160)
Scarlet Fever	May cause endocarditis and hypertension. Note late results (p 171)
Rheumatic Fever	May cause pericarditis endocarditis or myocarditis Get chest x ray and Ecg Note response to salicylate Consider pericardial aspiration if necessary (p 186)
Pneumococcus	May cause endocarditis pericarditis and bacteremia Get blood culture (p 199)
Meningococcus	May cause bacteremia and endocarditis Get blood culture (p 208)
Gonococcus	May cause bacteremia and endocarditis Get blood culture (p 217) and history of venereal infection
Typhoid Fever	May cause bradycardia and myocarditis Get blood culture and Ecg (p 225)
Brucellosis	May cause myocarditis and endocarditis Get blood culture (p 314) and skin test.
C Diphtheriae	May cause myocarditis tachycardia and cardiac arrhythmia Get Ecg and throat culture (p 302)
H Influenzae	May cau e endocarditis and bacteremia Get blood culture (p 396)
M Tuberculosis	May cause tachycardia and adhesive pericarditis Get chest x ray sputum examination and skin test (p 252)
Syphilis	May cause myocarditis endocarditis and aortitis Chest x ray Ecg and serology tests (p 331)
Infectious Jaundice	Causes relative bradycardia
Trichinosis	May cause myocarditis Ecg and skin test (p 539)
Filariasis	May cause elephantiasis Examine blood smears at night (p 3321)
Tsutsugamushi Fever	May cause myocarditis and cardiac irregularities (p 381)
Periarteritis Nodosa	With peripheral vascular manifestations and skin lesions Note eosinophilia Biopsy (p 1027)
Uremia	With terminal pericarditis Note azotemia (p 2276)
Thyrotoxicosis	With tachycardia and irregularities, particularly in thyrotoxic crises Increased BMR and therapeutic response to iodine (p 1197)

CONTINUED

SYPHILIS OF THE CORONARY ARTERIES

Coronary artery disease in the syphilitic is more likely to be due to an incidental arteriosclerosis (p 983) than the specific process In the latter instance, the luetic arteritis usually accompanies an *aortitis* (p 1025) with or without *aortic insufficiency* (p 970)

Pathology—The coronary lesion of syphilis *involves the mouths of the vessels* more often the right and the adjacent 0 5 to 1 5 cm of the vessel wall The combination of *ostial stenosis* with insufficiency of the aortic valves constitutes a serious physiologic burden to the myocardium which usually develops great hypertrophy, later the muscle fibers undergo necrosis fibrosis or myelomalacia

Clinical Manifestations—The clinical manifestations of coronary syphilis rarely develop for ten to twenty years after the acquisition of the primary lesion Their variety may be infinite there may be *paroxysms of nocturnal dyspnea* (p 942) *anginal pain* (p 890) evidence of *coronary insufficiency* (p 895) constant *substernal pain* (p 892) episodes of *cardiac asthma*

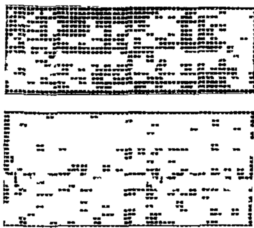


Fig 221—*Upper* Lead I 40 year old male with thrombo angutis obliterans and coronary thrombosis *Lower* Lead I same patient thirteen years later showing restitution to normal

attacks of *pulmonary edema* (p 810) and sudden unexpected *death* Congestive failure (p 941) is a late development and indicates a marked exhaustion of cardiac reserve

Examination usually reveals widening of the supracardiac portion of the aorta accentuation of the aortic second sound or the diastolic murmur of aortic insufficiency (p 970) The electrocardiogram gives evidences of left axis deviation The serological tests for syphilis (p 336) may be positive but often are deceptively negative

Treatment—The treatment of syphilis once vascular complications have arisen is hazardous and unsatisfactory It is doubtful whether the lesion can be benefited in any way In order to prevent the production of a Jarisch Herxheimer *reaction in the root of the aorta* with resultant acute closure and death a preliminary course of *iodides* (p 608) is given for several weeks thereafter a course of at least 10 000 000 units of penicillin with bismuth supplementation (p 126) offers the most hope with the least risk (p 340)

Myocardial Infarction	From coronary occlusion With precordial pain Electrocardiographic changes leukocytosis and increased edimentation rate (p 983)
Cerebral Hemorrhage and Thrombosis	With or without localizing motor and sensory changes (p 1439)
Backward Failure	Usually with pulmonary hypostasis (p 941)
Thrombophlebitis	With or without localizing symptoms and signs (p 1124)
Embolization	With or without localizing symptoms or signs (p 208b)
Sinus Thrombosis	Usually secondary to adjacent infection of kin eye ear nose or accessory nasal sinuses (p 2130)
Lymphangitis and Lymphadenitis	From drainage of infected areas (p 3962)
Acute Disseminated Lupus Erythematosus	With associated non bacterial endocarditis (p 3395)

ACUTE FIBRINOUS PERICARDITIS

Acute fibrinous pericarditis may be encountered as the result of bacterial or nonbacterial irritations of the serous lining of the cardiac sac

Etiology—Acute fibrinous pericarditis occurs as a complicating lesion in *rheumatic fever* (p 186) and *pneumococcal pneumonia* (p 2171) It is seen as a terminal event in *azotemia* (p 2276) and accompanies *myocardial infarction* resulting from coronary occlusion (p 983)

Pathology—Fibrinous pericarditis may occur in a localized area as exemplified by the myocardial infarcts it may involve the entire epicardial and pericardial surfaces as in acute rheumatic fever Under any circumstance the involved area loses the normal glistening appearance and becomes dull and opaque fibrin is deposited until in the more advanced instances the entire serous surface is covered with a shaggy exudate Small amounts of free fluid are present in the late stages the effusion overshadows the fibrinous process giving rise to the clinical picture of a hydropericardium (p 1009)

Clinical Manifestations—The characteristic physical sign of a fibrinous pericarditis is the presence of the *friction rub* that is usually best heard near the left border of the sternum the sound appears near to the surface and is increased by pressure of the stethoscope Typically it is heard in systole and diastole giving the characteristic *to and fro* quality at times only a systolic or diastolic component may be present

The pericardial friction rub is transitory it usually lasts for only a few hours but may persist for several days

During the acute process whether the underlying condition is infectious or noninfectious there are constitutional manifestations such as elevation of temperature leukocytosis and tachycardia Patients often complain of local pain and tenderness

Rheumatic Pericarditis—The fibrinous pericarditis of rheumatic fever rarely constitutes the only manifestation of the infection more often it is detected after the febrile episode has been established for several weeks At the time of the complicating pericarditis the heart rate becomes more rapid the respiratory rate increases without corresponding dyspnea a

Clinical Manifestations—The beriberi heart is often *asymptomatic* at the other extreme it may be the cause of *sudden death* In the intermediate examples there are often subjective complaints such as progressive *dyspnea palpitation* or attacks of *cardiac irregularity cyanosis* is frequently observed precordial distress and tenderness are occasional complaints

The objective findings are usually disproportionately advanced compared with the patient's complaint The heart is *almost invariably* enlarged due to *hypertrophy* and *dilatation* of the chambers the blood pressure is low the *electrocardiogram* is characterized by low voltage of QRS and T waves Arrhythmias (p 873) are of frequent occurrence and may be paroxysmal or *relatively constant the first apical sound may be reduplicated pulsus alternans* may be noted the heart rate is increased even at rest and the heart sounds are usually diminished (p 3542) Relative murmurs are often heard inevitably the manifestations of *backward failure* (p 941) *are superimposed* (wet beriberi) (p 623)

In addition to the circulatory signs the patient presents other manifestations of the *avitaminosis* (p 616)

Diagnosis and Treatment—The diagnosis of beriberi heart is often established by the *therapeutic test* The patient often an alcoholic (p 3848) or one on a markedly deficient diet (p 581) reveals a phenomenal degree of improvement when given intravenous injections of *thiamine chloride niacin* and *riboflavin* or *oral doses of a potent B complex* (p 622)

PARASITIC MYOCARDITIS

Myocarditis is one of the striking manifestations of severe *trichinosis* (p 539) *often it is the cause of death the patient succumbing to progressive* backward failure (p 941) In these instances autopsies reveal the presence of the parasite within the cardiac musculature In life this eventuality is suggested by the electrocardiographic changes

Less frequent than the myocarditis of trichinosis is that due to the *cysticercus* (p 1899) of *Taenia solium* The development of myocardial disturbances in the patient with a known intestinal infestation suggests the possibility that this rare complication has occurred

SYPHILITIC MYOCARDITIS

Despite the frequency with which syphilis involves the aorta myocardial lesions are rare *Gummas* have been described as clinical rarities the diagnosis being suggested by the presence of *heart block* (p 879) positive serological evidences and the response to the administration of iodides (p 608)

TUBERCULOUS MYOCARDITIS

Tuberculous myocarditis may occur in the course of a *general miliary invasion* (p 261) The cardiac lesion is masked by the symptoms of the dominant meningeal or pulmonary invasion It requires no special therapy and has only academic importance

FIEDLER'S MYOCARDITIS

The term Fiedler's myocarditis was employed in olden days to indicate an idiopathic type of progressive myocardial degeneration It is

febrile increase is experienced often the patient notes an unproductive dry cough and sharply localized precordial pain (See p 892)

In some instances the onset is misleading with severe epigastric pain In the presence of fever and leukocytosis the resultant syndrome simulates an acute abdominal disturbance

Tuberculous Pericarditis—The fibrinous exudate of tuberculosis rarely causes a significant disturbance since the effusive element next to be described dominates the picture

Pneumococcic Pericarditis—Fibrinous pericarditis is of frequent occurrence in pneumococcus pneumonia The friction rub is often ephemeral and sharply localized Pneumococci are present in the exudate which is highly infectious and may progress to suppuration (p 1010)

Azotemic Pericarditis—The patient with chronic nephritis and azotemia (p 2276) often develops a terminal fibrinous pericarditis Repeated auscultation rarely fails to disclose the characteristic friction rub which constitutes an important prognostic sign indicating the onset of the preagonal stage

Myocardial Infarction—The infarcted myocardial area is often the site of an overlying aseptic fibrinous pericarditis The presence of the friction rub is of important diagnostic significance (p 3549)

Diagnosis—The diagnosis of fibrinous pericarditis is essentially a clinical discipline radiographic confirmation is absent at most the electrocardiographic changes include an elevation of the S T segment low voltage and a diphasic or inverted T wave (p 806)

The differential diagnosis of fibrinous pericarditis requires that the underlying etiologic factor be elucidated In the absence of manifestations of rheumatic fever or a pneumococcal pneumonitis the practitioner suspects the possible aseptic causes of azotemia and coronary thrombosis If the presence of these latter conditions is not apparent through the obvious clinical features a blood chemical analysis (p 3712) and an electrocardiographic tracing should soon settle the disputed point

Course—The course of fibrinous pericarditis is toward recovery in the vast majority of instances Under these circumstances the rub and the accompanying constitutional manifestations disappear In the minority of patients the fibrinous process is followed by effusion (p 1008) and under these circumstances the friction rub disappears but the cardiac silhouette becomes progressively enlarged as the sac fills with fluid

Treatment—Specific treatment of fibrinous pericarditis is accomplished by the salicylates in rheumatic fever (p 186) and penicillin (p 106) in pneumococcal infections Desperation and probatory antibiotic therapy (p 114) merits trial using penicillin sulfonamides (p 88) and/or streptomycin (p 103) Symptomatic relief may be afforded by an ice-cap to the precordium or by opiates

SEROUS PERICARDITIS (PERICARDIAL EFFUSION)

Serous pericarditis is essentially a progression of the fibrinous process The etiologic agencies are most often *rheumatic fever* (p 186) *and the tubercle bacillus* (p 252) rarely effusive pericarditis is the result of *pneumococcal infection* (p 199) *azotemia* (p 2276) or *coronary thrombosis* (p 983)

Treatment—A prolonged period of quiet is necessary after a diphtheritic myocarditis This condition is one of the rare instances in which the practitioner must err on the side of conservatism and keep the patient at complete rest for several weeks or months after all acute manifestations have wholly and completely disappeared *Drug therapy is strictly avoided* unless there are definitive indications In particular *digitalis* is not administered since it can accomplish no good unless there are evidences of circulatory failure and it predisposes to the development of irregularities The uses of the alleged *cardiac stimulants* (caffeine strychnine epinephrine camphor and camphor derivatives such as cardiazol and metrazol) constitute meddlesome treatment with potential danger out of all proportion to possible benefits The application of the *ice bag* over the precordium is a routine that is time honored it is physiologically unsound but may be good psychotherapy

The management of convalescence is exceedingly difficult The child is given sedatives if necessary and *massage* and *passive motion* (p 3766) precede any active attempt to exercise (p 3757) *Rehabilitation* and *re education* of the musculature (p 3756) require the most expert supervision

Rheumatic Myocarditis

The myocarditis of acute rheumatic fever is probably an accompaniment of every attack of this insidious infection Aschoff nodules are demonstrable almost without exception in children who succumb to rheumatic fever There seems little doubt but that the cardiac manifestations constitute a *pancarditis* at all times

Clinical Manifestations—In the course of acute rheumatic fever the clinical diagnosis of myocarditis becomes apparent when the *small signs* of muscular involvement present themselves These are more apparent by quantitative than gross qualitative alterations The *pulse rate* increases *blood pressure* falls *cardiac murmurs* or *irregularities* are noted, constitutional symptoms particularly fever and leukocytosis increase the *sedimentation time* becomes more rapid *dyspnea* is more annoying and the child s face reveals *anxiety* and *distress* Electrocardiographic changes include prolongation of the P R interval **(ECG 45)** P wave changes and right axis deviation in mitral stenosis **(ECG 21 to 27)** left axis deviations in preponderant aortic disease and the various irregularities particularly auricular fibrillation **(ECG 65, 70, 71)**

Treatment—The sudden death that characterizes diphtheritic myocarditis fortunately does not often occur in rheumatic fever Nevertheless the insidiousness of the changes and the delayed myocardial manifestations constitute an ever present threat The efficacy of the *salicylates* is purely symptomatic the drug neither prevents nor relieves the myocardial affliction As in diphtheria cardiac drugs are avoided unless there are definitive manifestations of a functional disturbance that may possibly yield to their action

Thiamine Chloride Deficiency (Beriberi Heart)

Vitamin B deficiency (p 623) is associated with myocardial insufficiency probably due to a hydropic degeneration of the muscle fibers

Clinical Manifestations —A pericardial effusion of less than 200 or 300 cc is difficult to detect by physical examination Amounts in excess of this produce progressive increase in the area of *cardiac dullness* and progressive diminution in the intensity of the *heart sounds* With larger amounts of fluid the right border of the heart appears displaced the *cardiohepatic angle* which is normally at 90 degrees is obliterated *shifting flatness* is demonstrable at the base of the heart an area of increased dullness fremitus and bronchial breathing is noted in the left interscapular area (*Ewart s sign*) a *pulsus paradoxus* is observed in that the cardiac rate slows and the radial pulse decreases in volume on inspiration instead of in the expiratory phase With large effusions evidences of *cardiac tamponade* (p 872) are observed dyspnea and orthopnea increase the blood pressure falls terror dreams and delirium occur often the patient sleeps with head resting on a bed table

In children a *precordial bulge* is noted Pressure of the sac on mediastinal structures may cause *hiccough cough aphonia* or *dysphagia*

Pericarditis of Rheumatic Fever —The pericarditis of rheumatic fever occasionally dominates the clinical picture when fluid accumulates with great rapidity This phase is accompanied by constitutional manifestations such as elevation of temperature tachycardia and leukocytosis The effusion reacts specifically and characteristically to the administration of *salicylates* (p 383-2) this fact often serving as a therapeutic test

Pericarditis of Tuberculosis —The nonrheumatic pericardial effusions of inflammatory nature are most often tuberculous In contrast to the rheumatic variety the tuberculous effusion is slow in its development It causes remarkably little cardiac embarrassment and does not recede under salicylate therapy

Diagnosis —The earliest diagnosis of pericardial effusion is made from the roentgenographic examination Fluoroscopy or films show a generalized increase in the size of the cardiac shadow with a blunting of the contours In the right anterior oblique position an early sign of effusion is the obliteration of the right postero-inferior recess the right cardiophrenic angle becomes acute cardiac pulsations diminish and appear shallow and wavelike the cardiac configuration changes with alteration from the upright to the recumbent position

Electrocardiographic Changes (ECG 16, 17, 46) —Acute pericarditis produces changes in the serial electrocardiographic tracings There is first an elevation of the R S T segment in all leads which is strikingly different from the reciprocal effect exhibited by Leads 1 and 3 in an acute myocardial infarction (p 992) The T waves are usually upright and tend to be higher than previously the amplitude of QRS may be diminished in all leads

Later the electrocardiogram shows a return of the R S T segment and the T wave toward normality after which low voltage in the QRS complexes develops with flattening or inversion of T waves

Aspiration —The diagnosis of a pericardial effusion is definitely established by the diagnostic tap (p 852) which is most safely executed in the fourth right interspace at the left sternal border in the sixth or seventh interspace posteriorly in the midst of the area of greatest flatness or episternally

The endocarditis may in severe types of the disease involve the chordae tendinae and the walls of the ventricle and auricle especially of the left auricle just above the valve The subsequent scarring results in a valve defect (p 970) infrequently resolution of the acute inflammation may be complete

Microscopically there is formation of new vessels and a proliferation of the cells of the myocardial *tschoff nodule* invasions of the endocardium on top of healed lesions is characteristic

Clinical Manifestations—In 20 to 30 per cent of the children with rheumatic heart disease there is no antecedent history of rheumatic fever *Often the first evidence of the disease is the finding of the murmur on* routine physical examination (p 973) In the more obvious instances the child with a clearly recognizable attack of rheumatic fever develops an impurity and later a murmur at a valvular orifice In subsequent attacks the *murmur may* become intensified or additional evidences of valvulitis are superimposed

The physical signs of valvular deformity are always associated with those related to the *pancarditis The commoner definitive findings include* persistent tachycardia abnormalities in rhythm changes in quality and intensity of the first apical sound a blowing systolic murmur heard best at the apex enlargement of the heart impurity of sound in the period of *diastole reduplication of* the first apical sound accentuation of the first apical sound impurity of the second aortic sound a blowing diastolic murmur heard just to the left of the sternum in the third fourth or fifth interspaces and the later development of peripheral manifestations of aortic insufficiency to include high pulse pressure the water hammer pulse and the presence of capillary pulsation

The commoner *electrocardiographic abnormalities* are prolongation of the P R *interval and* serial changes in the QRS the ST and the T waves Serial roentgenograms often depict progressive increase in the size of the cardiac shadow or a change in contour toward mitralization (p 798) or left sided hypertrophy (p 795) At times the clinical picture is dominated by the *pericardial reaction* which may be fibrinous (p 1007) or effusive (p 1008)

Many children with the rheumatic syndrome fail to show cardiac abnormalities of significant degree during the acute phases of the inflammatory process When reexamined at later periods the evidences of valvulitis become progressively more manifest Estimates of the extent of the *circulatory impairment in rheumatic fever must be deferred for many* months

Diagnosis.—See Table 67 p 1018

Course and Prognosis—On rare occasions the rheumatic endocarditis heals without producing significant mechanical defects of the valve More often the patient is left with an *insufficiency* or *a stenosis* The dangers and sequels of valvular deformities are elsewhere discussed (p 970) In the *present place it is sufficient to emphasize that they predispose to* congestive failure (p 941) attacks of acute coronary insufficiency (p 895) angina pectoris (p 890) and the superimposition of a subacute bacterial endocarditis (p 1021)

Treatment.—The complication of a rheumatic endocarditis requires the

Bact al Vacc ne made f om the Plague Bacillus N N R
For the prevention of plague (p 3°)

Bact r al Vaccine made f om Typho d Bac llus U S P
For the prevention of typhoi l fever (p 236)

Bacter al Vaccine made f om Typhoid Bac llus and the Paratypho d A and B Bacill U S P
For the prevention of the enteric fevers with *Eberthella typho a* and the Salmonellae

Old Tubercul n U S P
For diagnosis by intracutaneous or cutaneous injection or by the patch method (p 262)

Typhus Vaccine
For tl e prevention of typhus fever (p 37o)

Rocky Mounta n Spotted Fe V cc ne
For tl e prevention of Rocky Mounta n spotted fe r (p 380)

Yellow F er Vacc ne
An attenuated l ving virus suspension (p 480)

Smallpox Vaccine U S P
An attenuated living virus for tl e prevention of smallpox (p 447)

Equine Encephalitis Vaccine
A virus suspension for the prevention of equine encephal tis (p 451)

Measles Vaccine
For the prevent on of measles (p 415)

Cold Vaccine
Useless preparation (p 2118)

Catarrhal Vaccines
Useless preparation

St Louis Encephalitis Vaccine
Irradiated attenuated vaccine used experimentally for p ophylax s (p 457)

Infl enza A and B Vacc ne
Of great potential value in influenzal infections (p 397)

Poliomyel tis Vaccine
Irradiated attenuated vaccine used experimentally for prophylaxis (p 464)

Technic of Active Immunization—Vaccine or toxoid therapy varies in its execution with the individual remedies In general the practitioner should carefully read and meticulously follow the directions printed with each commercially available preparation

ROUTES OF ADMINISTRATION—Active immunization may be carried out by the oral intracutaneous or subcutaneous routes *Oral vaccine* has been used particularly with typhoid and the unofficial cold vaccines The oral route has only the advantage that the patient may employ self medication and reactions are conspicuously absent It is not recommended in clinical practice since the results are uncertain and the benefits of typhoid immun ization are too important to deal with in a casual manner

Intracutaneous immunization is increasing in favor Remarkably ef fective results are obtained from the use of relatively small amounts since it is rarely possible to use more than 0 1 to 0 2 cc at a single site of injec

the action of the toxin but does not destroy it Freezing a mixture of diphtheria toxin antitoxin for example liberates the active toxin from the mixture

Under certain conditions of temperature time and chemical environment some toxins lose their toxicity but retain their antigenic powers Thus there are formed the *toxoids* which are valuable agents for immunization to the toxins from which they are derived Diphtheria and tetanus toxoids are widely used

ANTIGENS EMPLOYED IN CLINICAL MEDICINE

(Boldface type indicates preparations of indubitable and proven efficacy)

Rabies Vaccine U S P
An uncontaminated suspension of the attenuated dry or dead fixed virus of rabies (p 439)

Scarlet Fever Streptococcus Toxin U S P
For immunization and the performance of the diagnostic Dick test (p 183)

Diphtheria Toxin U S P
For the performance of the diagnostic Schick test (p 303)

Diphtheria Toxin Antitoxin Mixture N.N R
For active immunization (p 309)

Diphtheria Toxoid U.S P
For active immunization against diphtheria

Diphtheria Toxoid Alum Precipitated U S P
A refined preparation for diphtheria immunization

Tetanus Toxoid Alum Precipitated U S P
For active immunization against tetanus (p 296)

Diphtheria Toxoid Tetanus Toxoid Alum Precipitated Combined N N R
For combined active immunization against diphtheria and tetanus

Pertussis Vaccine N N R
Highly promising preparation for the prevention of whooping cough (p 283)

Diphtheria Toxoid Alum Precipitated Whooping Cough Vaccine Combined N N.R
For simultaneous active immunization against whooping cough and diphtheria

Diphtheria Toxoid Tetanus Toxoid Alum Precipitated Whooping Cough Vaccine Combined N N R
For simultaneous immunization against diphtheria tetanus and whooping cough

Staphylococcus Toxoid N.N.R
For active immunization in staphylococcal infection

Staphylococcus Vaccine N.N.R
For active immunization against staphylococcal infection (p 157)

P Tularensis Vaccine
For prevention of tularemia (p 325)

Bacterial Vaccine made from Brucella N.N.R
For the prevention and treatment of undulant fever (p 319)

Bacterial Vaccine made from the Cholera Vibrio N N R
For cholera prevention (p 250)

impossible in the present era to state with accuracy whether this constituted a *specific clinical entity* or was more likely a manifestation of coronary artery sclerosis (p 983)

RHEUMATIC ENDOCARDITIS

Rheumatic endocarditis is the commonest form of heart disease that is *observed in childhood* It is responsible for fully 90 per cent of the defective hearts seen in the young and about 30 per cent of the damaged hearts in the older age group

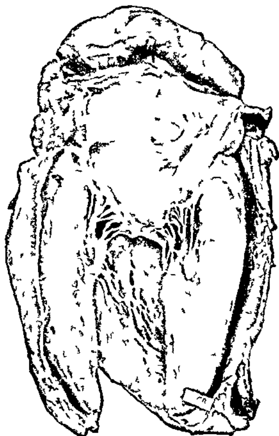


Fig 222 —Verrucose rheumatic vegetations on the mitral valve Subacute and chronic pericarditis with adhesions *

Pathology —The acute inflammatory reaction of the valve is the production of vegetations of fibrin (*verrucae*) which form thrombi The verrucae are adherent and small in contrast with the vegetations of subacute bacterial endocarditis (p 1021) they do not embolize and when removed leave a raw underlying surface They are distributed to form rows on the auricular surfaces of the cusps of the mitral and tricuspid valves and on the ventricular surfaces of the semilunar valve cusps at the lines of closure

* MacCallum Textbook of Pathology

tima The involved vessel may be diffusely inflamed or it may show spotty areas of inflammation The latter gives the vessels a nodular appearance to which the disease owes its name The inflammatory process eventually weakens the walls local aneurysms form with rupture and hemorrhage producing bizarre symptoms and often a fatal termination

Clinical Manifestations—Periarteritis nodosa occurs more often in the male It is usually a prolonged illness with a fatal outcome The disease exhibits the phenomena of general infection with bizarre localized phenomena The patient is septic febrile asthenic and anemic The more persistent complaints include diffuse myalgias and arthralgias

The localizing symptoms cover the range of clinical medicine *cardiac phenomena* include those of acute coronary insufficiency acute coronary

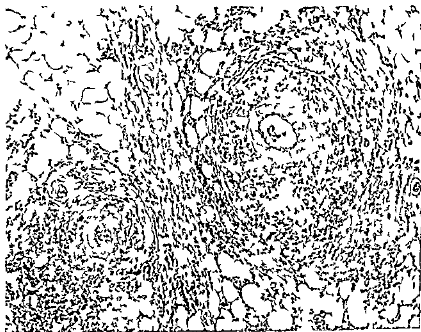


Fig 225—Periarteritis nodosa showing infiltration of walls of arterioles *

closure hypertension localized aneurysms There may be *pulmonary manifestations* such as asthma pleurisy pulmonary infarctions or episodes of bronchopneumonia The *renal symptoms* are those of glomerulo nephritis infarctions retroperitoneal hemorrhage or malignant sclerosis there may be *abnormal urinary findings* including albumin casts white and red cells The *gastro intestinal manifestations* are those of ulceration hemorrhage perforation and peritonitis there may be evidences of gastritis ileitis hepatitis with jaundice or symptoms suggesting an appendicitis The *neurological manifestations* include peripheral neuritis convulsions or a syndrome that suggests encephalitis *Ocular lesions* are iridocyclitis retinal exudates and hemorrhages or involvements of choroidal vessels There may be fluid in the pericardium pleura and peritoneum

Various *dermatoses* are observed these include purpura urticaria a

* MacCallum Textbook of Pathology

gical approach however the present outlook is highly optimistic Because of the gravity of the affliction combined therapy is recommended with *sulfonamide* (p 88) *streptomycin* (p 103) and *penicillin* (p 106) *Heparinization* (p 1050) as in subacute bacterial endocarditis may be highly advisable

Preoccupation with the medical program of therapy must not deter the practitioner from seeking the site of the infective focus and summoning *surgical consultation* for its drainage or eradication Infected veins should be ligated and excised abscess cavities are evacuated and drained a gangrenous part may require amputation

SUBACUTE BACTERIAL ENDOCARDITIS (ENDOCARDITIS LENTA)

Subacute bacterial endocarditis is a prolonged insidious infection involving previously damaged heart valves It is characterized by the signs and symptoms of a general infection valvulitis embolic phenomena and bacteremia

Etiology—The organism responsible for most examples of subacute bacterial endocarditis is the *Streptococcus viridans* other invaders are the *H influenzae* or the *gonococcus*

Pathogenesis—Rheumatic valvular disease preexists in about 80 per cent of the patients Congenital cardiovascular defects especially bicuspid aortic valves septal defects coarctation of the aorta and patent ductus arteriosus are other important predisposing conditions Rarely a luetic aortitis or atherosclerotic valve may be affected

The mechanism by which bacteria become lodged on the deformed valve and by which the vegetations develop has not been determined A direct blood stream infection of the endocardium may be due to circulating streptococci the organisms may reach the endocardium through the blood vessels in the valves

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The vegetations have a tendency to heal so that fresh vegetation and fibrosing lesions coexist occasionally there is also evidence of active rheumatic fever Tiny abscesses (*Bracht Wachter lesions*) are sometimes found in the myocardium Microscopically the vegetations consist of few platelets and fibrin with masses of bacteria on the surface of the vegetation The valve itself is infiltrated by mononuclear cells but there are no polymorphonuclear leukocytes The bacteria may be deep within the mass of platelet fibrin

diffuse erythematopapular eruption edema of the face ulcers of the mouth and subcutaneous nodules that are elevated dusky red and covered with a slight scale The nodules may become necrotic and ulcerate they may rupture and produce a localized ecchymosis or a hematoma when they heal there is local atrophy

A suggestion of the diagnosis is sometimes made by the blood count which reveals a marked leukocytosis There may be as many as 40 000 to 60 000 white blood cells with a moderate *eosinophilia* A secondary anemia eventually develops the blood cultures are sterile unless there is a terminal bacteremia

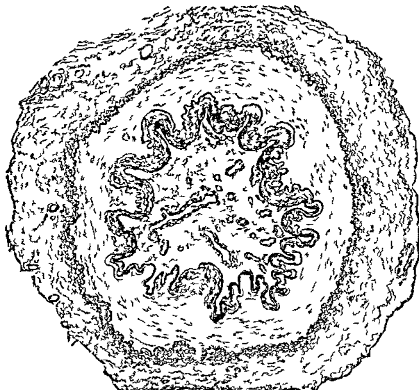


Fig 26—Obliterating endarteritis (thrombo-obliterans) with shrinkage of the walls and partial recanalization

Diagnosis—When the diagnosis of periarteritis nodosa is suspected a local lesion is taken out for histologic study In no other way can the definitive opinion be hazarded

Treatment—Treatment is symptomatic

THROMBO ANGIITIS OBLITERANS (BUERGER S DISEASE)

Thrombo angiitis obliterans is a thrombo inflammatory disorder involving the peripheral arteries and veins It may become sufficiently extensive to produce gangrene

MacCallum Textbook of Pathology

Course —The course of atypical verrucous endocarditis is progressively unfavorable Eventually there is a terminal bacteremia with death due to azotemia progressive toxemia or circulatory failure Treatment is un satisfactory though intensive chemotherapy using the *sulfonamides* (p 88) and *penicillin* (p 106) without or with heparin, should be given thorough trial as in subacute bacterial endocarditis (p 1021) Protection from solar radiation is required, as in lupus erythematosus (p 3396) In desperation injections of gold may be tried (pp 2922, 3396)

NONBACTERIAL THROMBOTIC ENDOCARDITIS

Nonbacterial thrombotic endocarditis is essentially a pathological en tity which occurs as a terminal complication in many chronic diseases such as *nephritis* (p 2373) *diabetes* (p 1246) and *cancer* (p 572)

The *pathogenesis* of the condition is unknown the lesions may be toxic or bacterial they consist of small vegetations of the rheumatic type

The *presence of nonbacterial thrombotic endocarditis is seldom sus pected during life*, it has only academic significance since *treatment is ineffectual*

ACUTE BACTERIAL ENDOCARDITIS

In acute bacterial endocarditis there is a direct implantation of bac teria on the heart valves with demonstrable bacteremia

Etiology —The common infecting organisms in acute bacterial endo carditis are the *Streptococcus haemolyticus* the *pneumococcus* the *Staph ylococcus aureus* and the *gonococcus* Other bacteria, rarely found include the *meningococcus* the *typhoid bacillus* the *enterococcus* and the *Bru cella melitensis*

The infection may occur in a sound heart or one that has been the previous site of a rheumatic lesion (p 186) or a congenital defect (p 953)

Pathology —The characteristic features of acute bacterial endocarditis are large exuberant friable *vegetations* with partial destruction and ul ceration of the valves and the chordae tendineae or mitral and aortic valves There may be involvement of the pulmonary valves The vegetations which may be implanted at the site of a congenital abnormality consist of irregular masses of fibrin leukocytes and colonies of bacteria Mycotic aneurysms occur and embolic pyemic abscesses are frequent complica tions Occasionally pyemic abscesses of the heart muscles are due to cor onary embolism with the infected thrombi

Clinical Manifestations —The symptoms of acute bacterial endocarditis are those of an overwhelming general infection with local manifestations due to the embolic involvement of an organ The temperatures are high and spiking *Tachycardia general prostration* and evidences of *sepsis* are present, valvular involvement is suspected when *cardiac murmurs* appear the *spleen* enlarges, *embolic phenomena* and *petechiae* are noted Occa sionally a spread taken from a petechia reveals the organism

There is usually a *leukocytosis* unless the infection has been so ful minant that a leukopenia has developed instead Blood cultures are per sistently positive

Diagnosis —See *Differential Diagnosis of Endocarditis* (p 1018)

Treatment —In the presulfonamide era recovery from an acute bacte rial endocarditis was rarely encountered With chemotherapy a sur

Etiology—The etiology of thrombo angiitis is unknown The patients are usually heavy smokers (p 3884) and are made worse by smoking many have epidermophytosis (p 3293) and are sensitive to fungus extracts The suggested etiologic relationships of the streptococcus, the rickettsia of typhus and ergotism from rye bread remain unproven

The disease is almost exclusively a male affliction It occurs disproportionately in Jews but may appear in any group

Pathology—Arteries and veins are occluded by soft thrombi which in later stages become organized and recanalized The lesions are segmented and patchy They occur more often in the legs and may involve the coronary vessels

Clinical Manifestations—The typical sufferer is a *male* under the age of fifty he is generally addicted to *tobacco* Often there are repeated episodes of *migratory phlebitis* followed by attacks of *arterial occlusion* and periods of *remissions*

The prodromal symptoms are persistent *coldness* in one or both extremities Aching *pain* develops first after exercise and then at rest in digits ankles instep wrist or forearm In addition to evidences of *migratory phlebitis* tender red areas appear in the skin overlying the valves of the superficial veins Small irritations cause ulceration of the part which shows changes in color the ache becomes a pain which is present at rest and made worse by exercise Night pain robs the patient of sleep and he then smokes even more excessively

In the severer instances the ulcer becomes necrotic and *gangrenous* it spreads until a whole part becomes involved and if it does not spontaneously slough may require amputation

Examination reveals evidences of *vessel occlusion* The pulses cannot be felt, *oscillometer readings* are depressed or absent elevation of the part causes pallor and dependency produces red cyanosis Skin temperatures are lowered the muscles become wasted and atrophic and functional tests reveal arterial spasm followed by occlusion Coronary thrombosis may result in myocardial infarction (Fig 226 p 1029)

Course—The disease takes various forms In most instances the progress is slow Occasionally through revascularization the changes regress and disappear Rarely an acute fulminating example progresses rapidly to severe gangrene and the extremity must then be amputated

Diagnosis—Thrombo angiitis obliterans may be confused with peripheral occlusive arteriosclerosis (p 994) The latter occurs in the older age group of fifty five to eighty five years as contrasted with twenty five to forty five years for Buerger s disease Superficial phlebitis quite common in thrombo angiitis is rare in arteriosclerosis the ulcers in Buerger s disease tend to be moist whereas in arteriosclerosis they are usually dryer In the latter condition rest pain is not nearly so common as in thrombo-angiitis In practically all instances of thrombo angiitis the patient has been an inveterate smoker

Treatment—Thrombo angiitis obliterans may be a self limited disease Its progress can be modified by proper medical control Essentials are the absolute prohibition of tobacco avoidance of cold and trauma skin cleanliness and treatment of the dermatophytosis (p 3307) The faithfulness with

gical approach however the present outlook is highly optimistic Because of the gravity of the affliction combined therapy is recommended with *sulfonamide* (p 88) *streptomycin* (p 103) and *penicillin* (p 106) *Heparinization* (p 1050) as in subacute bacterial endocarditis may be highly advisable

Preoccupation with the medical program of therapy must not deter the practitioner from seeking the site of the infective focus and summoning *surgical consultation* for its drainage or eradication Infected veins should be ligated and excised abscess cavities are evacuated and drained a gangrenous part may require amputation

SUBACUTE BACTERIAL ENDOCARDITIS (ENDOCARDITIS LENTA)

Subacute bacterial endocarditis is a prolonged insidious infection involving previously damaged heart valves It is characterized by the signs and symptoms of a general infection valvulitis embolic phenomena and bacteremia

Etiology—The organism responsible for most examples of subacute bacterial endocarditis is the *Streptococcus viridans* other invaders are the *H influenzae* or the *gonococcus*

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The vegetations have a tendency to heal so that fresh vegetation and fibrosing lesions coexist occasionally there is also evidence of active rheumatic fever Tiny abscesses (*Bracht Wachter lesions*) are sometimes found in the myocardium Microscopically the vegetations consist of few platelets and fibrin with masses of bacteria on the surface of the vegetation The valve itself is infiltrated by mononuclear cells but there are no polymorphonuclear leukocytes The bacteria may be deep within the mass of [illegible]let fibrin

which the sufferer carries out therapeutic recommendations is a determining factor in the outcome of the medical regimen

General Measures—The measures described for the treatment of peripheral vascular disease are carried out (p 997) The patient is kept in bed during periods when the disease is active he forswears tobacco completely and permanently

Attempts to Increase Circulation—The circulation is stimulated by *postural exercises* (p 998) *reactive hyperemia* (p 997) and the application of *heat* to the involved limbs In addition the physician may use intravenous injections of *hypertonic saline solution* giving 250 to 350 cc of a 5 per cent solution two to three times weekly The circulatory status also may be improved by *intravenous typhoid vaccine* (p 1379) given once or twice a week for six to eight weeks by intermittent venous occlusion by intermittent suction and pressure in the pavex boot and by contrast baths

Drug Therapy—*Alcohol* (p 3847) *papaverine* (p 3859) and *demerol* (p 3863) are adjuvant drugs for their vasodilator action as in the treatment of arteriosclerotic peripheral vascular disease (p 997) Prolonged administration of *sulfonamide* seems to have occasional efficacy Sulfadiazine may be given in doses of 4 to 4.5 gm (60 to 67½ grains) daily for a two week period After a rest period of two weeks a second course of the drug is given before attempting to evaluate the efficacy of the chemotherapeutic endeavor

NOT RECOMMENDED—The value of the *anticoagulants* has not yet been demonstrated Preparations which have been given adequate trial without consistent favorable results include *parathyroid* and *thyroid extracts* *aminophylline* the *iodides* *estrogen* *androgen* the *tissue extracts* and *sodium thiosulfate*

Treatment of Pain—With severe pain the patient is entitled to vigorous therapy which is instituted in order The simple *analgesics* (p 3894) are given later *codeine* is added courses of *demerol* are attempted *alcohol* and *papaverine* are administered in increasing dosage and *hyperthermia* is produced by intravenous injection of *typhoid vaccine* (p 1379) A check is made on the possible use of tobacco Bed rest is of course mandatory

When all other measures fail *alcohol injection* into the peripheral nerves or a posterior nerve root block by paravertebral injection may be necessary

Treatment of Gangrene—In the presence of frank gangrene the patient is put to bed with a thermoregulated heat cradle set for about 90 F (32 2° C) The wound is covered with light sterile dressings and a sulfonamide powder Pressure is avoided by a cradle which supports the bed clothes After weeks or months the gangrenous part may slough Thereafter the wound granulates and may heal aided at times by the use of stimulating substances such as cod liver oil and zinc salve (p 3132)

Massive gangrene of an extremity generally requires amputation below the knee Amputation of the toes is rarely followed by healing whereas amputation of the fingers is usually successful

Sympathectomy—Sympathectomy to increase blood supply should

In addition to the cardiac lesions other vascular abnormalities include mycotic aneurysms arteritis of the smaller vessels and embolisms The *kidney* may show glomerular lesions of a focal embolic type a diffuse nephritis or an infarction the *spleen* is much enlarged and often is infarcted

Clinical Manifestations —The *onset* of subacute bacterial endocarditis is usually insidious Most patients begin with indefinite symptoms such as lassitude asthenia and sweating Later it is noted that fever is also pres

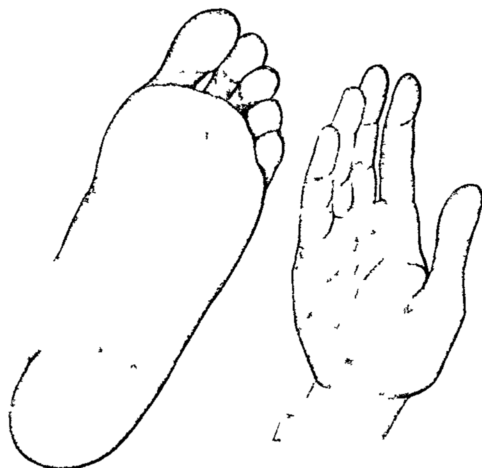


Fig 224—Subacute bacterial endocarditis active stage Janeway lesions

ent Occasionally the onset is sudden with embolic phenomena and renal or splenic infarction There are frequent chills the temperature may range between normal in the morning to 103 or more in the evening the weight decreases an anemia develops splenomegaly is noted and the valvular murmurs become intensified or fresh evidences are heard

The kidney may be subject to minute emboli which produce microscopic hematuria (p 2306) Occasionally diffuse glomerular nephritis is present and the clinical findings may be predominantly nephritic

Libman and Friedberg The Oxford Medicine Oxford University Press

not be performed without evaluating the functional element in the disease Skin temperatures are measured before and after the use of a vasodilating agent such as intravenous typhoid vaccine If the skin temperature rises only insignificantly sympathectomy can result in little benefit but if the temperature rises considerably the operation may help

PHLEBITIS

See p 1124

LYMPHANGITIS

See p 3962

LYMPHADENITIS

See p 3962

TEMPORAL ARTERITIS

Temporal arteritis is a rare inflammatory disorder affecting primarily but not exclusively the temporal arteries It occurs between the ages of 55 and 65 and is twice as common in women

The outstanding feature of the syndrome is severe almost constant pain chiefly temporal often accompanied by fever photophobia diplopia and visual disturbances Characteristically a segment of one or both arteries becomes prominent indurated nodular and tender If symptoms do not subside the involved vessel should be resected

Diffuse bone and joint tenderness also may be present Occasionally there is tenderness on percussion over the lower portion of the sternum Clubbing of the fingers and toes frequently occurs after the first few weeks and may recede if the endocarditis heals or passes into the bacteria free stage

The Skin —The appearance of the skin is unique and may be diagnostic The patient develop a peculiar tan tint described as *cafe au lait* the local skin lesions may be petechial Osler nodes Janeway nodes or splinter hemorrhages may be noted

PETECHIAE —The petechiae are pinhead sized slightly oval and hemorrhagic lesions with white centers they occur most commonly on the conjunctival sac and in the oral mucosa on the palate and occasionally in the supraclavicular region They disappear after several days and tend to come in crops They must not be confused with traumatic hemorrhages in the mouth or small hemangiomas in the conjunctival sac

Petechiae though common in subacute bacterial endocarditis may also occur in other conditions such as Libman Sacks disease (p 1019) various of the hemorrhagic diatheses (p 1108) leukemia (p 1100) metastatic malignancies (p 572) and septicemia (p 54) The exact nature of these lesions is not understood whether they represent an arteritis embolic phenomena or a combination of the two has not yet been definitely settled

OSLER NODE —The Osler node is tender reddish slightly raised and pea sized it usually appears on the tips or sides of the fingers subungually or on the thenar or hypothenar eminences At times it may have a purplish color Osler lesions last for several days to a week like petechiae the exact cause of the Osler node is not understood but it is attributed similarly to arteriolitis and embolization

JANEWAY LESION AND THE SPLINTER HEMORRHAGE—The Janeway lesion occurs in many patients with subacute bacterial endocarditis In contrast to the Osler node the Janeway lesion is never tender it consists of a small red or hemorrhagic area measuring from 1 to 4 mm across and occurring frequently on the soles palms and tips of the digits *Splinter hemorrhages* occur beneath the nails where they resemble small red splinters they are frequently tender on pressure

Laboratory Findings —The presence of two consecutive *positive blood cultures* establishes the diagnosis of subacute bacterial endocarditis An isolated positive blood culture is inadequate evidence as transitory bacteremia has been reported in nonspecific conditions A sterile blood culture does not rule out the condition if the vegetations are limited to the right heart and the bacteria are filtered out first in the lungs the blood cultures may be negative

Secondary anemia is almost constant The white count varies but generally is normal or slightly elevated however leukopenia may be present counts of 25 000 are noted particularly after widespread embolization Moderate polynucleosis with an increase in immature forms may occur

Of some diagnostic value is the appearance of *macrophages* in the peripheral blood These are large leukocytes somewhat resembling monocytes and may constitute 30 to 40 per cent of the white cells They are best observed in the first drop of blood obtained from the puncture of the ear lobe

INDEX

NOTE Boldface p ge numbers indicate main discussions

Diagnosis—See *Differential Diagnosis of Endocarditis* (p 1018)

Treatment—Previously, a disease which progressed inexorably to fatality subacute bacterial endocarditis now yields to chemotherapy by the method described by Loewe

Chemotherapy and Heparinization (Loewe)—The Loewe method of treatment consists of isolation of the causative organism and testing of its sensitivity to *penicillin* and *streptomycin* The majority of organisms yield to the former substance by *continuous intravenous drip* (p 3775) or intramuscular deposit in massive dosage At least three weeks of treatment is favored employing as many as 10 000 000 Oxford units of the antibiotic substance At the onset of therapy *heparinization* (p 1051) is accomplished by the subcutaneous implant of this substance using the menstruum described by Loewe An initial dose of 300 to 400 mg is placed in the region of the fascia lata blood coagulation studies are made two or three times daily the injection of heparin requires repetition at two three or four day intervals

The practitioner is warned that there are many difficulties associated with the Loewe therapy To preserve the efficacy of the penicillin ice bags are required to be packed around the containing cylinders the rate of flow must be reduced to 1 to 2 cc per minute elevations of temperature are frequently due to the heparin and must not discourage the continuation of the treatment local pain is frequent from the heparin deposit and may require the use of opiates

Eradication of Foci of Infection—Before discharge of the patient foci of infection are eradicated In most instances this requires *tonsillectomy* or *tooth extraction* (p 1663) Preoperatively the patient is given a large dose of *penicillin* and immediately following operation the substance is applied to the raw surface by topical application

Course—In the majority of the successfully treated patients, the temperature falls within a few days the blood cultures become sterile the patients exhibit a phenomenal sense of well being and are soon able to leave the hospital They may resume their normal duties if the valvular defect has not too greatly handicapped the circulation

The recent introduction of the Loewe treatment makes it impossible to predicate the future course of these patients If they are reinfected or suffer infectious relapse the treatment may be repeated but this should not entail any particular technical difficulty Thus far therapy has not provoked the complication of embolizations nor have there been untoward consequences as the result of the increase in the bleeding time

Obsolete Methods—The success of the Loewe treatment has rendered obsolete other forms of therapy which included massive sulfonamide administration and hyperthermia in association with chemotherapy

SYPHILITIC ENDOCARDITIS

Syphilitic endocarditis is almost invariably an *aortic* lesion giving rise to an *insufficiency* of the valve (p 970) The earlier teaching of the corollary of this statement namely that aortic insufficiency is most often syphilitic is not in accordance with present clinical observation since rheumatic lesions considerably outnumber the luetic

See *Differential Diagnosis of Endocarditis* (p 1018)

The clinical manifestations of aortic insufficiency (p 970) are else where discussed The treatment of the syphilitic valvulitis follows along the lines indicated in syphilitic aortitis (p 1026)

SYPHILITIC AORTITIS

The basic pathologic lesion of cardiovascular syphilis is uncomplicated syphilitic aortitis or its aneurysmal complication Less often associated aortic valvulitis and coronary arteritis (p 1026) are observed as secondary phenomena

Incidence —In private practice syphilitic aortitis and aneurysm are infrequently observed The condition is said to occur with greater fre quency in the underprivileged where it may constitute a significant proportion of the amount of cardiovascular invalidism

Pathology —Invasion of the aortic walls undoubtedly occurs during the early stages of infectious syphilis With involvement of the sinuses of Valsalva the aortic ring may dilate with the production of valvular in sufficiency (p 970) the ostia of the coronary arteries may be narrowed with resultant embarrassment of the blood supply to the myocardium (p 1015)

The histological lesions of syphilitic aortitis resemble those of the process elsewhere there is an obliterative endarteritis of the vasa vasorum with perivascular round cell infiltration in the adventitia Degenerative changes occur in the media the elastic layer shows interruption and frag mentation of its fibers Eventually there is connective tissue replacement with thickening and hyalinization of the intima

The intima appears characteristically creased and furrowed It exhibits irregular sunken areas beneath which the wall of the aorta is thinner than elsewhere The arch elongates and dilates focal weakness of the wall leads to the formation of the saccular aneurysm Characteristically the lesion stops short just beneath the diaphragm in contrast to the distribution in arteriosclerotic aortitis (p 993)

Spirochetes are demonstrable in sections of the wall of the aorta

Clinical Manifestations of Syphilitic Aortitis —This condition is *asympto matic* for a decade or longer The diagnosis is established by the clinician when he observes in a seropositive individual a broadening of the supra cardiac shadow There may or may not be evidences of aortic insufficiency (p 970) and manifestations attributable to insufficiencies of the coronary circulation (p 995)

The earlier subjective complaint is usually a sense of *substernal op pression* or *pain* Less often the patient notes paroxysms of *nocturnal dyspnea* or *orthopnea*

When the signs of aortitis are closely investigated the attendant phys ician may observe elongation and dilatation of the arch *increased pulsa tions* in the suprasternal arch a smaller carotid or radial pulse on one side than the other a *systolic thrust* and *diastolic shock* felt best over the sternum increase in *substernal dulness* a systolic bruit over the aortic arch and accentuation of the aortic second sound with an amphoric tambour or bell like quality

If the patient is not definitively arteriosclerotic and there are other physical signs and serologic evidences of syphilis the diagnosis is estab lished with a reasonable degree of clinical certainty

The practitioner avoids two serious errors the complement fixation test may be positive in only 80 per cent of individuals with syphilitic aortitis and the patient with Wassermann positivity may have an arteriosclerotic aortitis which is unrelated to his venereal infection

Syphilitic Aortic Valvulitis—Syphilitic aortitis is frequently associated with syphilitic aortic valvulitis Under these circumstances the characteristic insufficiency murmur is heard in association with the peripheral phenomena elsewhere described (p 970)

Syphilitic Coronary Arteritis—Syphilitic aortitis may be associated with syphilitic coronary arteritis *Under these circumstances the ostia are* markedly narrowed the right being involved as frequently if not more often than the left branch The presence of evidences of coronary insufficiency (p 895) angina pectoris (p 890) acute coronary closure (p 983) myocardial infarction (p 992) myocardial fibrosis and myomalacia (p 993) suggest that the luetic aortitis is complicated by involvement of the blood vessels of the heart

ANEURYSM

The aneurysm of the thoracic aorta is formed when the wall weakens and distends producing the characteristic sac Whereas arteriosclerosis frequently produces a diffuse dilatation of the aorta the saccular aneurysms *are almost invariably complications of syphilitic aortitis*

Pathology—The syphilitic aneurysmal sac most commonly springs from the convexity of the arch the orifice is round or irregular in outline the edge is rolled over into it so as to overhang its cavity The latter may reach great size pushing aside the surrounding organs or imbedding itself in them in a variety of ways Mechanical symptoms are produced by pressure on the *recurrent laryngeal nerve* (p 1488) the *trachea* the *lungs* the *bronchi* (p 2047) the bony structures of the *thorax* (p 2046), the *ribs* or the *esophagus* Thrombus formation occurs in the sac so that the phenomena of *embolization* are frequently encountered the sac may *rupture producing a dissecting aneurysm or sudden death*

Clinical Manifestations—The thoracic aneurysm is *asymptomatic* for a considerable period of time It may first be noted on routine physical examination The suggestive signs include *visible pulsation* in the suprasternal notch or in the upper right interspaces an *expansile bulging* in these regions a *systolic thrill* and *diastolic shock* over the aneurysmal sac a rough systolic murmur followed by a snapping sound coincident with closure of the aortic valve, roentgenological demonstration of small sacculations, fluoroscopic observation of localized areas of *expansile pulsation* in antero posterior or lateral views (p 799)

At times the presenting phenomena are due to disturbances of adjacent structures They include compression of the innominate artery with diminution in the size of the radial artery *atelectasis* from compression of the right bronchus or lung compression or deflection of the trachea with the characteristic *tracheal tug* hoarseness *brassy cough* and visible evidences of *cord paralysis* from involvement of the recurrent laryngeal nerve *dysphagia* from pressure on the esophagus *anisocoria* and *unilateral sweating* from involvement of the superior c ang

tion of the involuntary nervous system and *intractable spinal pain* from erosion of the vertebrae

The subjective symptoms of the aortic aneurysm may postdate the physical signs by many years They include local pain dyspnea cough hoarseness difficulty in swallowing attacks of nocturnal dyspnea episodes of angina pectoris manifestations of cardiac failure hemoptysis or the appearance of an expansile pulsating tumor of the chest wall

Diagnosis.—See *Arteriosclerosis of the Aorta* (p 993)

Course—The patient with thoracic aneurysm is in constant jeopardy Fragments of thrombus may break off producing embolization the sac may rupture producing sudden death and there may be a fatal termination from acute *coronary insufficiency or a progressive congestive failure*

Treatment—The treatment of the thoracic aneurysm is symptomatic Efforts may be made to control the process by the administration of *iodides* (p 608) injections of *bismuth* (p 128) can do no harm but probably accomplish little by way of affecting the underlying condition. *Arsenotherapy is hazardous (p 116) but repeated courses of massive doses* of penicillin (p 340) are indicated

Patients with intractable pain are entitled to *nerve block* by alcohol injection Attempts to obliterate the aneurysm by surgical procedures hold some promise *in expert hands*

PULMONARY ARTERITIS

Pulmonary arteritis may occasionally occur as a rare complication of *rheumatic fever* (p 186) *subacute bacterial endocarditis* (p 1021) *or syphilis* (p 331) More often pulmonary artery involvement is noninfectious

NONSPECIFIC ANGIITIS

On rare occasions systemic infection such as typhoid fever typhus lobar pneumonia influenza cholera subacute bacterial endocarditis scarlet fever syphilis and tuberculosis may be associated with evidences of peripheral arterial disease The attention of the patient is called to the disturbance by local pain due to vasospasm or thrombosis. These accidents are unusual and require prompt therapy (p 1124) to prevent peripheral *gangrene*

The use of heparin is suggested although it has not been utilized in the experience of the authors

VISCERAL ANGIITIS

See *Atypical Verrucous Endocarditis* (*Libman-Sacks Disease*) (p 1019) *Acute Disseminated Lupus Erythematosus* (p 3399) *Dermatomyositis* (p 3373)

PERIARTERITIS NODOSA

Periarteritis nodosa is a *rare systemic disease* which involves arteries veins and capillaries It appears to be an inflammatory process secondary to some precedent infection that involves other organs Bacteria are not demonstrable in the vessel walls and many of the manifestations suggest that the pathogenesis is related to allergy (p 547)

Pathology—The lesion of periarteritis nodosa is an inflammatory reaction that involves first the adventitia then the media and finally the in

Vaccine therapy should not cause serious *systemic manifestations* A certain amount of malaise headache and an inappreciable pyrexia (up to 1) are permissible The patient should not be made sick by the therapeutic injection unless speed is of the essence as occasionally happens with active contacts in diphtheria or scarlet fever

Artificially Acquired Passive Immunity

Passive immunity is produced by the parenteral injection of a serum that is rich in specific antibodies The antibodies may be directed against bacterial exotoxin bacterial endotoxin viruses or rickettsia *Homologous antiserum* is obtained from human beings convalescent from certain of the acute infectious diseases *heterologous antiserum* is derived from an animal usually a horse or rabbit which has been actively immunized with the specific antigen Heterologous serums may be antitoxic or anti parasitic

Passive immunity is temporary It evokes little cellular response but its chief virtue lies in the speed with which it exhibits its efficacy Agents for the production of passive immunity are of definite value in prophylaxis but their curative worth is less well established They may be combined with chemotherapeutic and antibiotic agents whose ease of administration and efficacy promise almost total eclipse of immunotherapy

Autohemotherapy—Despite its wide popularity in Europe autohemotherapy is a disappointing procedure It requires the removal of 20 cc of blood from a vein and immediate intramuscular injection before clotting has taken place It has no demonstrable rationale and actually serves no purpose so far as we have been able to ascertain It is most widely employed in the treatment of *chorea* (p 190) *urticaria* and *asthma* (p 2101) It is our opinion that autohemotherapy has only psychotherapeutic value

Plasma Fractionates—There is increasing recognition of the importance of plasma and of the elucidation of the efficacy of many of its fractions Present advices (Janeway J.A.M.A *126*:674 1944) indicate that yields of plasma include the following

1 *Serum Albumin* packaged so that each 100 cc contains 25 gm of serum albumin and 1 7 per cent of sodium chloride in a 1 10 000 concentration of merthiolate Injected intravenously the concentrate increases serum albumin and the colloid osmotic pressure of the patient s plasma As a result there is a rapid transfer of fluid from extravascular to vascular compartments with increase in plasma volume fall in hemoglobin and hematocrit readings and alleviation of the manifestations of *forward failure* (*shock*) Serum albumin also is useful in the medical treatment of *edema* and *hypoproteinemia* The preparation is stable and easily transported it does not require reconstitution cross matching or other preliminary testing reactions are virtually unknown The dose of 25 gm may be repeated at fifteen to thirty minute intervals The conscious patient is encouraged to drink water with salt in order to compensate the deficit of fluid and saline

2 A *gamma globulin fraction* available for injection in the prevention and treatment of *measles* (p 416) Injections are given preferably on the fifth day after exposure A dose of 0 1 to 0 75 cc. per pound affords complete protection Smaller doses given at other than the optimum time may result in modification of measles so that it is a mild infection Reactions to intramuscular injection consist of local soreness and some elevation of

tion The vast majority of vaccines are given *subcutaneously* *Intramuscular* and *intravenous injections* are apt to cause serious constitutional disturbances

REACTIONS TO ACTIVE IMMUNIZATION —Vaccine therapy produces local focal and systemic reactions

The *local reactions* consist of the usual inflammatory manifestations of redness heat swelling and pain The practitioner should attempt to produce a tangible but not excessive local reaction The dose can only be ascertained by the individual method of trial and error An optimum local reaction is one in which the patient is not too seriously inconvenienced or pained and in which the objective phenomena are not excessive that is that they do not extend beyond the circumference of perhaps a silver dollar

If an excessive local reaction has been produced the practitioner does well to diminish succeeding doses even if it is necessary to add an addi

TABLE 10 —TIME TABLE FOR ACTIVE IMMUNIZATION IN CHILDHOOD

3 to 6 months	Smallpox vaccine
6 to 12 months	1 cc of diphtheria toxoid tetanus toxoid alum precipitated whooping cough vaccine combined
2 weeks later	1 cc of whooping cough vaccine
2 weeks later	1 cc of diphtheria tetanus whooping cough combined as above
18 to 24 months	Schick test and booster dose of diphtheria toxoid alum precipitated if *necessary*
2 to 4 years	Scarlet fever immunization if demanded not favored by author
5 to 6 years	Booster dose of diphtheria toxoid or scarlet fever toxin if Schick or Dick test respectively is positive
8 to 12 years	Typhoid vaccine repeat smallpox

tional injection to the usually recommended course Thus typhoid immunizations are as well carried out with four injections as with three

If the patient does not obtain a significant local reaction and the dose administered is not the maximum recommended dose the amount may be stepped up to a maximum recommended dose but no higher Thus in the use of autogenous vaccines it is wise to start with 0 1 cc intracutaneously to test the skin sensitivity If there is not an excessive reaction the next injection should continue the intracutaneous dose and add 0 1 cc subcutaneously Guided by the local reaction the practitioner increases the subcutaneous amount by 0 1 cc increments to 1 cc

Focal reactions to vaccine therapy may be specific or nonspecific Thus the injection of an autogenous staphylococcic vaccine may cause a lighting up of the symptoms of a furuncle of the kidney This would be manifest by the appearance of pyuria local pain tenderness and fever Such a response need not necessarily be considered as particularly noxious However if a nonspecific infection particularly tuberculosis is activated the situation is indeed serious The further use of the vaccine is contraindicated

the disturbance was established as an icterogenic virus probably unrelated to the virus of the yellow fever With the elimination of human serum from yellow fever vaccine there have been no additional examples

The clinical syndrome of homologous serum jaundice bears some resemblance to epidemic hepatitis or acute infectious jaundice (p 1070) The patients usually recover in 6 to 8 weeks without perceptible sequels In fatal instances death occurs 3 to 6 weeks after onset The *incubation period* is 12 to 20 weeks *treatment* is wholly symptomatic

Heterologous Antitoxic Serum—Heterologous serums are obtained from horses rabbits goats and cattle Horse serum is most economical since the yield is greater Patients who are sensitive to horse serum may be given rabbit serum or one derived from cattle or goats

The protection derived from the serum is short lived since antitoxins are relatively rapidly excreted or destroyed within 3 to 6 weeks Antitoxic serums are of unquestioned efficacy in the active treatment of invasion particularly when the micro-organism is not susceptible to sulfonamide or the antibiotic agencies Antitoxic serums may be used in conjunction with anti infective therapy Because of the great efficacy of the latter and the easier administration of the remedies serotherapy is being employed to lesser and lesser degree (p 112)

HETEROLOGOUS ANTITOXIC SERUMS

(Boldface type indicates preparations of indubitable and proven efficacy)

Ant ven n (Crotalus) N N R.
Of value in the treatment of bites of rattlesnakes and moccasins (p 3190)

B t l sm Ant to n N N R.
Worthy of trial in the treatment of botulism (p 313)

D phther a Ant tox n U.S.P
Horse bovine and globulin modified preparations available and of proven valu in the treatment of d phtheria (p 309)

Erysipelas Streptococcus Antitoxin N.N.R.
Of little value since the introduction of sulfonamides and penicill n

Gas Gangrene Antitoxin (*Cl perfringens* and *Cl septicum*) N.N.R
Pr ferably use tetanus combined as below (p 300)

Gas Gangrene Polyvalent Antitoxin (*Cl perfring ns Cl s pticum Cl novyi Cl b fermentans* and *Cl histolyticum*) N.N.R
Preferably use tetanus combined (see below)

Tet us-Gas Gang e e Ant to (*Cl perfringens Cl septicum* and *Cl tetan*) N N R
Of definite value in anaerobically infected wounds (p 296)

Meningococcus Ant toxin N.N.R.
Superseded by sulfonamide and penicillin therapy

Sca let Fever Streptococcus Antitoxin U.S.P
May be used with sulfonami le and pen cill n therapy (p 1ff)

Staphylococcus Antitoxin
Superseded by sulfonamide and pen cillin therapy

Tet n s Ant tox n U.S.P
Preferably use gas gangrene combined (p 296)

temperature in 17 per cent of the cases The globulin has no value in *chickenpox* (p 420) but gives promise in *infectious hepatitis* (p 1979)

3 *Fibrin film with thrombin* containing fibrinogen and betaglobulin is used in surgery as an absorbable hemostatic agent It controls oozing in neurosurgery but is not recommended for the management of a brisk hemorrhage This tissue reaction to fibrin foam with thrombin is negligible The preparation may have value too in the control of hemorrhage in *hemophilia* (p 1118)

4 *Fibrin film* used in the repair of dural defects

5 *Isohemagglutinins* employed for blood grouping (p 3705)

6 Other fractionates as yet to be isolated and tested

Homologous Serums—Serum obtained from convalescent human beings may be pooled under aseptic conditions for use in the treatment of certain of the infectious diseases

AVAILABLE HUMAN HOMOLOGOUS PREPARATIONS FOR THE PRODUCTION OF PASSIVE IMMUNITY

(*Boldface type indicates preparations of indubitable and proven efficacy*)

Human Scarlet Fever Immune Serum USP
May be used in conjunction with sulfonamide and penicillin (p 166)

Human Measles Immune Serum or Globulin U S P
Of definite transitory value in modifying or attenuating the attack of measles (p 416)

Mumps Immune Serum
Of some value in immediate prophylaxis (p 484)

Pertussis Immune Serum
Of some value in prophylaxis (p 283)

Poliomyelitis Immune Serum
Worthy of trial for lack of more potent specific therapy (p 464)

Chickenpox Immune Serum
Not worth the trouble of injection

Yellow Fever Immune Serum
Of proven value (p 480)

Rocky Mountain Spotted Fever Immune Serum
Worthy of trial (p 380)

Anti tularemia Immune Serum
Worthy of trial (p 395)

Anti plague Serum
Worthy of trial (p 399)

Reactions to Homologous Serums—Human serum does not sensitize the subject and for the most part the only untoward reactions are occasional urticaria and slight elevation of temperature The serious complicating reaction of homologous serum jaundice has been encountered in the use of yellow fever vaccine

HOMOLOGOUS SERUM JAUNDICE—The most serious example of homologous serum jaundice occurred in 1942 after the use of certain lots of yellow fever vaccine for the armed forces Approximately 29 000 examples of jaundice were encountered with 62 deaths from acute hepatitis The origin of

the disturbance was established as an icterogenic virus probably unrelated to the virus of the yellow fever With the elimination of human serum from yellow fever vaccine there have been no additional examples

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Superseded by sulfonamide and penicillin therapy

Scarlet Fever Streptococcus Antitoxin U.S.P

May be used w th sulfonamide and penicillin the apy (p 166)

Staphylococcus Antitoxin

Superseded by sulfonam de and pen cillin the apy

T t nus Ant to n U S P

Preferably use gas gangrene combined (p 296)

Tetanus Antitoxin Bovine

For use in patients who are sensitive to horse serum

Pertussis Antitoxin Rabbit

Lyophiled hyperimmune serum is reported of considerable value (p 283)

Heterologous Antibacterial Serums—The antibacterial serums are of less demonstrable value than the antitoxins Except under unusual circumstances their use is not recommended in infections by organisms that are sensitive to sulfonamide or penicillin

ANTIBACTERIAL SERUMS AVAILABLE FOR PASSIVE IMMUNIZATION

(Boldface type indicates preparations of indubitable and proven efficacy)

Anti anthrax Serum N N R

Retain as remedy of desperation if sulfonamide and penicillin fail (p 293)

Anti dysentery Serum N N R

Of occasional value in conjunction with soluble or insoluble sulfonamide (p 217)

Anti erysipelas Serum N N R

Superseded by sulfonamide and penicillin

Anti erysipeloid Serum N N R

Superseded by sulfonamide and penicillin

Anti meningococcic Serum U S P

Superseded by sulfonamide and penicillin

Anti pneumococcic Sera U S P

For types I II I and II IV and VIII V and VII VIII also rabbit sera for types I to XXXII inclusive with the exception of IX VII XIV XXVI and XXX superseded by sulfonamide and penicillin (p 218)

Anti tularemia Serum (horse goat)

In experimental use May be superseded by streptomycin (p 104)

Anti influenza B Serum (rabbit)

Of value in meningitis in conjunction with sulfonamide (p 286)

Anti typhus Serum

Experimental

Anti Rocky Mountain Spotted Fever Serum

Worthy of trial (p 380)

Anti brucellosis Serum

Worthy of trial (p 319)

Anti infectious Jaundice Serum

Less promising than penicillin

Anti plague Serum

Said to be useful (p 372)

The Administration of Serum—Serum may be given intravenously intramuscularly or intrathecally *Intramuscular injections* are used in infancy due to the difficulty of making the intravenous injection There is a delay in the concentrations of antibody but this is offset by the lesser possibility

of the production of a serum reaction The outer aspect of the thigh at the *junction of the upper third and lower two thirds is a favorable site* Absorption may be delayed by the application of a tourniquet above the level of the injection

Intrathecal injection has been virtually abandoned in the serum treatment of infections However the method may be employed in dealing with a sulfonamide or penicillin resistant organism The serum is given slowly by the gravity method after the removal of a slightly greater quantity of cerebrospinal fluid Intrathecally administered serum produces irritation and a resultant pleocytosis that may be mistaken for an exacerbation of the original infection

Intravenous serum injections are indicated in patients who are severely ill and who require maximum benefit in minimum time The injection must be made slowly in order to anticipate and prevent reactions If it is possible the intravenous drip technic (p 3775) is advisable and the cautious practitioner keeps at hand a syringe of 1 1000 epinephrine for administration at the first sign of difficulty Heterologous serum reactions may be primary or atopic they may assume the character of serum sickness or an acquired serum allergy

The *primary or atopic serum reaction* is an immediate anaphylactic like shock (p 540) that may be extremely severe or even fatal It occurs immediately after or even during the injection in the individual who is naturally sensitized to horse serum It is most apt to occur in patients who come of allergic families or who themselves have manifestations of allergic phenomena (p 547)

Serum disease develops in non allergic or normal individuals who have *never been sensitized previously to serum Serum sickness develops after* an incubation period of eight to twelve days It is characterized by fever skin manifestations usually of the urticarial type adenopathy and joint pains It may be mitigated and relieved by anti histamines (p 564)

Serum sickness does not endanger the life of the patient It is a distinct nuisance and may last from an average of four to six days to several weeks

The production of serum sickness is not in any way to be attributed to any lack of knowledge or precaution on the part of the practitioner It occurs in one-third of all individuals It may be relieved or ameliorated by anti histamines (p 564) and adrenergens (p 3877)

Acquired serum allergy occurs in patients who have previously received serum injections and developed serum sickness When they require reinjection of serum for some fresh and newly acquired infectious process the acquired serum allergy occurs

Acquired serum allergy may be of the *immediate type* consisting of serum sickness occurring after a day or two or it may be a localized or *Arthus like reaction* at the site of the reinjection

Acquired serum allergy not only comes on much sooner than serum sickness but it is apt to be more severe and may even prove to be fatal In consequence the patient *who gives a history of previous serum injection* and previous serum sickness should be desensitized no matter what the skin and eye tests show The nuisance and delay *of desensitization* are minor compared to the risk of an immediate severe or even fatal reaction

The Arthus phenomenon like manifestation of acquired serum allergy consists of a marked inflammatory local swelling and induration often with an extensive necrosis and slough at the site of the reinjection

Tests for Sensitivity—Prior to the injection of any therapeutic serum the patient is to be tested for sensitivity to the injectible substances Since the majority of these are horse sera most manufacturers supply sets containing a small vial of diluted serum for testing in the conjunctival sac (eye test) and between the layers of the skin (intracutaneous test) If such test materials are not available the serum itself should be diluted 1 10 and the test carried out in the usual manner

For the *ophthalmic test* 1 or 2 drops of the dilute serum are placed in the conjunctival sac In a positive reaction within 10 minutes there is redness and suffusion as compared to the other eye which is used as a control The instillation of 1 drop of epinephrine (1 1000) allays any severe reaction

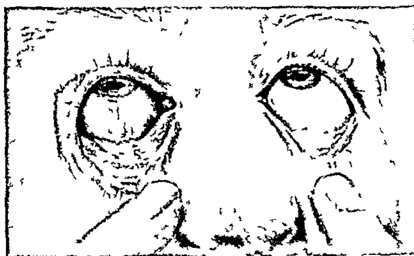


Fig. 13—Ophthalmic test Positive reaction in right eye

A positive reaction to a 1 10 dilution in the ophthalmic test calls for desensitization and a slow infusion of the diluted serum when the therapeutic amount is to be injected

For the *skin test* the 1 10 dilution of serum is injected intracutaneously in an amount of 0 02 cc The reaction is read in 10 minutes Any positive result calls for the greatest caution as indicated above

The Prevention of Serum Reactions—Serum reactions are prevented *by desensitization* the use of *anti histamines* (p 564) and a *continuous slow intravenous drip* (p 3775) *These three safeguards should be employed in every patient who* (1) *comes from an allergic family* (2) *gives a history of allergic manifestations* (3) *has had a previous injection of immune serum* (4) *exhibits a positive eye test* (5) *exhibits a positive skin test*

These precautions are certainly tedious but the practitioner since he is working on his own and with complete responsibility cannot hazard the slightest risk such as might be reasonable in an expert working with a complete staff in a well equipped hospital

Tuft Clinical Allergy

and for purposes of convenience their pharmacologic and therapeutic properties are discussed in the consideration of that disease in which they exhibit their most important function

MONOVALENT ANTI INFECTIVE AGENTS

Preparation	Specific Infection
Quinine	Malaria (p 507)
Quinacrine (Atabrine)	Malaria
Plasmochin	Malaria
Totaquine Chloroquine Pentaquine	Malaria
Gold	Atrophic arthritis (p 2922)
Salicylate	Rheumatic fever (p 186)
Iodine	Amebiasis (p 593)
Oxyquinoline Derivatives	Amebiasis
Emetine	Amebiasis
Chalmoogra Oil Promin	Leprosy (p 273)
Miscellaneous Synthetics	Trypanosomiasis (p 531)

POLYVALENT ANTI INFECTIVE AGENTS

In contrast to the sharp specificity of the monovalent anti infective agents is the blanket coverage of sulfonamides streptomycin and penicillin and to a lesser degree by arsenic and antimony The sulfonamides and penicillin as a matter of fact are the bane of those who revere classification and the joy of the practitioner whose interest is the relief of clinical disturbances Originally the *sulfonamides* were regarded as specific for gram positive organisms but soon it became obvious that they were effective also against the meningococcus and the gonococcus Theoretically powerless against the bacillary invaders they showed striking therapeutic efficacy in the treatment of chancroid presumably impotent against virus infections they successfully controlled lymphopathia venereum

Even more remarkable in its disregard for classification is *penicillin* This substance has apparently little respect for the gram stain and exhibits its beneficial effects in staphylococcal meningococcal and gonococcal invasions With even less concern for bacterial morphology it is effective in coccal bacillary or spirochetal invasions and exhibits remedial effects as well in certain virus rickettsial and fungus infections

Preparations of the sulfonamides streptomycin and penicillin are described in detail in this introductory chapter Reference is made in the discussion of the individual infections in subsequent chapters to the practical details of therapeusis and the methods of administration

The material on the polyvalent anti infective agents is concluded with studies of arsenic bismuth mercury antimony silver and para amino benzoic acid

THE SULFONAMIDES

The sulfonamides are amides of sulfanilic acid The parent compound is *sulfanilamide* which consists of aniline with a sulfonamide group —SO N in the para position of the benzene ring The various derivatives contain substituted rings or radicals as indicated (Figure 14)

The bacteriostatic power of the sulfonamides depends upon the presence of sulfur in the *para* position of the benzene ring The para amino group is

INDEX OF ILLUSTRATIONS

NOTE Boldface indicates colored illustration

also essential for when it is replaced or shifted to the *meta* or *ortho* positions potency is lost The presence of the nitrogen atoms in the substituted rings diminishes the toxicity of the various compounds sulfadiazine which has two nitrogen atoms seems less toxic than sulfapyridine or sulfathiazole which contain single nitrogens in their respective rings

Acetylation—Acetylation of one of the hydrogens of the para amino group occurs within the body and reduces the antibacterial tendency The amount of acetylation differs with each drug and may vary for the same



A



B

Fig 15—Sulfonamide dermatitis *A* Purpuric eruption of face after sulfathiazole *B* Erythema nodosum of legs after sulfathiazole

drug in different individuals The problem of acetylation is of extreme importance in the choice of the sulfonamide It is necessary to consider the amount of acetylation in the blood and urine not only from the standpoint of loss of bacteriostatic activity but also with relationship to solubility The acetylated compound in the urine may be quite insoluble leading to crystalluria and urolithiasis medicamentosa These conditions predispose to the development of hematuria lessened secretion of urine and renal insufficiency

Streptococcus (p 18?)

Soluble sulfonamides exert a powerful prophylactic and curative action on hemolytic varieties resistant strains may be encountered the non hemolytic varieties of the organism are relatively insusceptible

Pneumococcus (p 206)

The soluble sulfonamides exert a powerful prophylactic and curative action resistant strains and fastness may be encountered

Meningococcus (p 216)

The soluble sulfonamides exert a powerful prophylactic and curative effect resistant strains and fastness may be encountered

Gonococcus (p ???)

The soluble sulfonamides exert a powerful prophylactic and curative effect resistant and fast strains may be encountered

Enteric Bacilli (p 2?5)

Typhoid and paratyphoid organisms are insusceptible bacillary dysentery may respond to soluble or insoluble preparations favorable reports have been issued in cholera in urinary infections the colon bacillus may be susceptible to large concentrations given over long periods of time

Mycobacteria (p 267)

Neither the bacillus of tuberculosis nor that of leprosy is susceptible to soluble or in soluble sulfonamides promin is used in experimental tuberculosis

Hemophileae (p 284)

The pertussis organism is insusceptible meningitis due to *H influenzae* may respond to high concentrations of the soluble sulfonamides in chancroidal infections the *H ducreyi* is particularly susceptible to prophylactic doses of the soluble sulfonamides

Anthrax (p 293)

The *B anthracis* is sensitive to the soluble sulfonamides

Clostridia and Corynebacteria (p 301)

The organisms of gas gangrene are but slightly susceptible to sulfonamide therapy the diphtheria organism is not sensitive to sulfonamide nor is the *Cl botulinum*

Brucelleae (p 320)

While there is no conclusive evidence that sulfonamides react on the organism of melitensi the insoluble preparations have been reported to cause favorable clinical results

Pasteurellae (p 3?1)

While the pasteurellae are not sulfonamide sensitive there are encouraging clinical reports of the effects of the soluble preparations against the *B pestis* of plague tularemia seems sulfonamide resistant

Glanders (p 3?7)

The *M mallei* of glanders seems sulfonamide resistant

Friedlander Bacillus (p 3?8)

The *K pneumoniae* seems sulfonamide resistant

Spirochetes (p 3?9)

Treponema borrelia leptospira and spirilla seem sulfonamide-resistant with the possible exception of the fusospirochetes of Vincent s infection

The Rickettsia (p 366)

None of the rickettsial infections seem to respond favorably to sulfonamide therapy

Viruses (p 38?)

In virus infection the sulfonamides seem to be of greatest value in the prevention of complications with sensitive coccal invaders effects on the primary pathogens how

one another and may exhibit synergism Their modes of action are apparently dissimilar since organisms which are susceptible to any one may be resistant to the others Certain invaders that have become fast to sulfonamide for example may be penicillin sensitive

The comparative efficacy of sulfonamide and penicillin requires pains taking *analysis by the clinician this subject is elaborated in greater detail* following the description of the antibiotic preparations (p 115)

Toxicity

In the experimental animal large doses of sulfonamide produce a state of depression of the central nervous system that resembles the effect produced by large amounts of ethyl alcohol In the clinic the toxic manifestations of central nervous origin include nausea vomiting drug fevers extreme mental confusion amnesia and acute psychoses The free SO_2NH group of the sulfanilamide molecule poisons the enzyme carbonic anhydrase which functions as a catalyst in the normal conversion of carbon dioxide to the bicarbonate ion *As a result of this the alkali reserve is reduced and* clinical acidosis may be produced

The therapeutic use of the sulfonamide compounds is attended by a high incidence of toxic reactions In most instances the untoward effects are mild and of minor consequence but serious and at times fatal reactions may be encountered There is a basic qualitative similarity with respect to the toxicity of the various members of the sulfonamide group The individual drugs however vary in the frequency with which they elicit these reactions In some instances the individual drugs give rise to specific toxic effects that are not encountered with the other compound At times the untoward effects are due to overdosage but again they may result from unforeseen and unpredictable idiosyncrasy

Nervous System —A large proportion of patients taking full doses of sulfonamides experience symptoms referable to the effects of the drug on the central nervous system The nervous symptoms may be encountered with any of the drugs but are most common with *sulfapyridine* and are least common with *sulfadiazine Dizziness tinnitus headache* and *malaise* are frequent the patient frequently acts as though *intoxicated depression confusion acute mania* and *delirium* are occasionally observed It is important to differentiate these symptoms from an *acute toxic psychosis* in the patient with a severe infection (p 1376)

Peripheral neuritis has been encountered It is rare when sulfanilamide is used but occurs more commonly with sulfathiazole a high incidence has been noted with other derivatives that have not been accepted for general use i e sulfamethylthiazole and sulfanyl sulfanilamide

Fever —The administration of the sulfonamides may cause a drug fever which alters the clinical picture in a confusing manner since recrudescence of infection may be suspected Drug fevers are common with *sulfapyridine* and occur somewhat less with *sulfanilamide* and *sulfathiazole sulfadiazine causes drug fevers in a smaller* number of instances

Drug fever is frequently associated with a *toxic dermatitis* and a mild *eosinophilia* The onset usually is abrupt at the end of the first week of treatment It has been encountered as early as the third or fourth day and as late as the thirteenth day Commonly the temperature ris-- -- ---

The white blood cells are often affected adversely by the sulfonamides The effect is comparatively late in contrast to the early onset of *acute hemolytic anemia* Most commonly a progressive *leukopenia* or *granulocytopenia* is encountered In rare instances an *acute agranulocytosis* may be seen during the third week of treatment Leukopenia such as occurs in severe pneumonia with bacteremia does not contraindicate treatment with the sulfonamides On the contrary intensive therapy is urgently indicated and as the infection is controlled the white count rises

The incidence of leukocyte depression in the adult is about equal after *sulfanilamide* and *sulfapyridine* The latter drug however is a frequent cause of extreme leukopenia in infants and children while sulfanilamide is the most common cause of acute hemolytic anemia *Sulfathiazole* and *sulfadiazine* are relatively non toxic in this respect Aplastic anemia has been encountered in a few patients treated with sulfonamides

Sulfathiazole and sulfadiazine both tend to produce mild pan leukopenia This is not necessarily an indication for stopping therapy unless there is evidence of a selective depression of the granulocytes

Liver Damage—Sulfanilamide and sulfathiazole may cause *toxic hepatitis* The liver damage is usually of a mild variety but an occasional acute yellow atrophy may develop Sulfapyridine and sulfadiazine are less hepatotoxic

Urinary Complications—Sulfapyridine and to a somewhat lesser extent sulfathiazole sulfadiazine and sulfamerazine produce acetyl derivatives whose relative insolubility in urine favors the occurrences of crystalluria sulfonamide calculi (urolithiasis medicamentosa) hematuria renal colic and an occasional obstructive anuria These complications appear to be greater with sulfapyridine and sulfathiazole

The occurrence of crystalluria is favored by dehydration and acidity of the urine The simultaneous administration of sodium bicarbonate or sixth molar sodium lactate increases the solubility of the sulfonamide acidity by increasing the urinary *p*H There is also evidence that sulfonamides are more active at a higher *p*H due to increased ionization

SULFONAMIDE PREPARATIONS

An almost infinite variety of compounds may be prepared from the basic nucleus of the sulfonamide formula For clinical purposes it is desirable to have soluble and insoluble products The *soluble sulfonamides* are intended for their post absorptive action throughout the tissues of the body in consequence they are potentially toxic under the best circumstances The *insoluble sulfonamides* are not intended for absorption through the mucosa of the intestinal tract and are used for their intra intestinal effects upon the bacteria in the fecal column and on the surface of the mucous membrane of the intestines and the colon

The Soluble Sulfonamides

The choice of the ideal soluble sulfonamide requires consideration of a variety of properties These include the distribution of the drug in the body tissues the percentage of blood acetylation the amount of excretion in the urine the percentage of urine acetylation the solubility of the acetylate the incidence of toxic symptoms and the efficacy of the anti infective agency against the invading parasite

Without tedious reference to the voluminous work that has been done on the many varieties of sulfonamide the practitioner may narrow his choice down to *sulfanilamide* *sulfathiazole* *sulfadiazine* and *sulfamerazine* He may exclude from his calculations *sulfapyridine* and *sulfamethazine* these products produce high acetylation frequent crystalluria and tendency to the formation of urinary calculi hematuria interference with renal secretion and efficiency considerable nausea and vomiting or uncertainty of anti infective action through acetylation The practitioner need hardly concern himself with *sulfacetamide* intended only for its urinary effects since high urinary concentrations of sulfonamide may be obtained from sulfanilamide sulfathiazole and sulfadiazine

The Choice of the Soluble Sulfonamide—The considerations summarized in Table 11 make it appear that *sulfadiazine* is the soluble sulfonamide of choice There seems little reason for resorting to *sulfapyridine* so far as systemic administration is concerned *sulfamerazine* the second choice has slightly higher toxicity but no greater therapeutic efficacy *sulfathiazole* rates consideration only against staphylococci gonococci and colon bacilli *sulfanilamide* may be retained in streptococcal infections and for topical use

It is our conviction that the practitioner faced with the problem of systemic sulfonamide therapy should utilize sulfadiazine reserving sulfamerazine as his second choice if difficulties arise or a successful therapeutic result is not obtained Sulfathiazole is regarded as a third choice and one which because of its high incidence of toxic dermatoses and its high percentage of urinary acetylation imposes a considerably greater hazard

To the roster of acceptable sulfonamides the Council on Pharmacy and Chemistry of the American Medical Association has added sulfapyrazine which appears to compare favorably with sulfadiazine and which has additional effectiveness against *S paradysenteriae* Its toxicity and dosages parallel those of sulfadiazine appreciable concentrations are produced in the cerebrospinal fluid A sodium salt is available for intravenous injection in 5 per cent solution

Promin (sodium P P diaminophenyl sulfone N N didextrose sulfonate) appears to have considerable value in the treatment of experimental tuberculosis in the guinea pig and in the control of leprosy

Administration and Dosage of Soluble Sulfonamides—The soluble sulfonamides may be applied locally or injected parenterally preferably by the intravenous route Most often they are given orally an advantage of considerable importance in the estimation of the relative practicability of sulfonamide as against penicillin (p 115)

Topical Application

Powder

Use sulfanilamide sulfathiazole or sulfadiazine in *sterile packaged* form

Solution

Aqueous microcrystalline sulfathiazole or sulfanilamide 4–8 gm in 30 cc of warm glycerin Sulfadiazine 2½ per cent W/V in Ethanolamines Solution (Pickrell) N.N.R

Without tedious reference to the voluminous work that has been done on the many varieties of sulfonamide the practitioner may narrow his choice down to *sulfanilamide sulfathiazole sulfadiazine* and *sulfamerazine* He may exclude from his calculations *sulfapyridine* and *sulfamethazine* these products produce high acetylation frequent crystalluria and tendency to the formation of urinary calculi hematuria interference with renal secretion and efficiency considerable nausea and vomiting or uncertainty of anti infective action through acetylation The practitioner need hardly concern himself with *sulfacetamide* intended only for its urinary effects since high urinary concentrations of sulfonamide may be obtained from sulfanilamide sulfathiazole and sulfadiazine

The Choice of the Soluble Sulfonamide—The considerations summarized in Table 11 make it appear that *sulfadiazine* is the soluble sulfonamide of choice There seems little reason for resorting to *sulfapyridine* so far as systemic administration is concerned *sulfamerazine* the second choice has slightly higher toxicity but no greater therapeutic efficacy *sulfathiazole* rates consideration only against staphylococci gonococci and colon bacilli *sulfanilamide* may be retained in streptococcal infections and for topical use

It is our conviction that the practitioner faced with the problem of systemic sulfonamide therapy should utilize sulfadiazine reserving sulfamerazine as his second choice if difficulties arise or a successful therapeutic result is not obtained Sulfathiazole is regarded as a third choice and one which because of its high incidence of toxic dermatoses and its high percentage of urinary acetylation imposes a considerably greater hazard

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the treatment of meningitis pneumonia and gonorrhea it is important that sulfathiazole and other sulfonamide preparations be used topically only when a specific need for them can be justified

The indiscriminate use of these preparations in minor conditions when less harmful drugs are adequate should be discontinued

Systemic Use—For systemic effect the *oral method* of administration is preferable for ambulatory patients and those who are not seriously or critically ill A very palatable product distinctly useful in childhood is cocoa flavored sulfadiazine or sulfathiazole in which each teaspoonful contains approximately 0 3 gm (5 grains) In an acute exigency it is wise to make an initial *intravenous injection* so that a satisfactory level is rapidly achieved Thereafter the maintenance dosage may be accomplished by oral doses started immediately the intravenous solution has been delivered

Several technical details require attention Glucose solutions should not be used as solvents for sulfonamide preparations as an inert sugar compound is formed The intravenous injection of the sodium salt of sulfathiazole or sulfadiazine is greatly to be preferred to *subcutaneous hypodermoclysis* the very slow intravenous injection of the 25 per cent sodium salts using a 26 gauge needle makes it possible to give the full amount in a 10 to 20 cc syringe otherwise with the 5 per cent solution it is necessary to set up an intravenous drip apparatus *Intrapleural* and *intrathecal* use of the solutions of sulfonamide is not particularly advantageous and certainly does not compare in efficacy with locally instilled penicillin Once again the practitioner is cautioned that sulfonamide powders and solutions are not sterile and require the same care in preparation and handling as any other agent used for introduction into the body

The Insoluble Sulfonamides

The available insoluble sulfonamides include *sulfaguanidine succinyl sulfathiazole* (*sulfasuxidine*) and *sulfathalidine* (*phthalylsulfathiazole*) The two former drugs have been accepted by N N R

Therapeutics—The insoluble sulfonamides are employed for their anti infective action in the prevention and treatment of bacillary dysenteries cholera and the nonspecific variety of colitis They are also used extensively in preoperative treatment preparatory to surgery of the large bowel Each of these preparations seems of considerable efficacy and current incomplete observations tend to favor *sulfathalidine* because of its lesser tendency to produce eruptions and its smaller dosage

Toxicology—Despite the relative insolubility of sulfaguanidine and kindred preparations relatively large amounts of sulfonamide are absorbed because of the very large dosages that are necessarily employed As a result the toxicologic phenomena that appear with the soluble sulfonamides are encountered also with the insoluble preparations Thus when 191 healthy carriers of the bacillary dysentery organisms were given a ten day course of sulfaguanidine in the amount of 10 5 gm daily 11 5 per cent developed complications of sufficient severity to necessitate discontinuance of the drug almost 10 per cent had *drug fever* 2 6 per cent had *toxicoderms* 2 1 per cent had significant *hematuria* and an additional 26 5 per cent had *crystalluria* The latter of itself is not considered a sufficient indication for cessation of the drug

DESENSITIZATION —The method of desensitization is as follows

1 Inject 0 05 cc of the therapeutic serum with 0 3 cc of epinephrine chloride 1 1000 subcutaneously
2 At half hour intervals repeat the above maintaining the epinephrine dosage at a constant but increasing the serum amounts to 0 1 cc 0 2 cc 0 5 cc 1 0 cc 2 0 cc 4 0 cc until the total amount has been given
3 *If the amount of serum to be injected is excessive and the local* immunization is proceeding too slowly a slow continuous intra venous drip may be set up (p 3775) as soon as the patient has received the 1 cc amount subcutaneously without reaction

CONTINUOUS INTRAVENOUS DRIP OF DILUTE SERUM —To administer the diluted serum in the intravenous drip the total dosage is dissolved in 10 parts of physiological saline solution or of 5 per cent dextrose in physi ological saline solution Commercially purchased sets are most adaptable for these purposes The serum may be removed from the container in a 20 or 50 cc syringe and injected into the bottle containing the diluent

The dilute serum is then introduced intravenously in the usual man ner (p 3775) the practitioner remaining in attendance and having readily available a syringe containing 1 1000 epinephrine solution In the event of systemic reaction the epinephrine solution is injected slowly into the rubber tubing of the drip in the vicinity of the needle

The use of the diluted serum by intravenous drip is perfectly safe Under laboratory conditions animals in an anaphylactic period may be given the specific antigen in large amounts with impunity provided only that the molecule is diluted 10 times and injected no more rapidly than 1 cc per minute

The Treatment of Serum Reactions—Serum reactions require symp tomatic relief Sedation is accomplished by sedatives particularly pheno barbital 15 mg (¼ grain) to which may be added an orally absorbed adrenergen such as ephedrine sulfate 25 or 50 mg (⅜ to ⅚ grain) Epinephrine 1 1000 may be injected in aqueous or oily solution and anti pruritic lotions or ointments may be applied locally (p 3349) The uses of histaminase (torantil) calcium salts and cevitamic (ascorbic) acid pro duce inconstant results at best despite enthusiastic claims of advocates of these measure but the anti histamines (p 564) are of specific value

Particularly dangerous are edemas which threaten the integrity of the airway through swellings of tongue uvula or larynx They may necessitate scarification or tracheotomy (p 3058)

ANTI INFECTIVE AGENTS

Anti infective agents must be capable of evoking potent damage to in vading parasites but little injury to the tissues of the host The affinity for the invading organism (*parasitotropism*) considered in relationship to the action of the agent on the cells of the host (*organotropism*) establishes the *chemotherapeutic index*

MONOVALENT AND POLYVALENT ANTI INFECTIVE AGENTS

The majority of the anti infective agents show marked specificity in their parasitotropism In this sense they may be regarded as monovalent

3 If a high blood level is required the blood sulfonamide level must be determined daily at least during the first week of therapy
4 The causative organism should be cultured from the body fluid or exudate before giving the drug If the clinical diagnosis is reason ably clear chemotherapy is started without waiting for the bac teriological report
5 The fluid balance should be accurately checked Fluids must be forced to maintain a daily urinary output of 1500 cc or more If the output falls much below this level the urine will tend to be come supersaturated and the drug will crystallize out in the urinary tract The administration of 2–4 gm (½ to 1 teaspoonful) of sodium bicarbonate with each dose decreases this tendency by alkalinization of the urine
6 The patient should have a hemoglobin determination leukocyte count and urinalysis before starting sulfonamide therapy at the end of the first day of treatment and at least twice a week there after Each urine specimen is to be observed grossly turbid or discolored voidings are kept for microscopic examination
7 Patients receiving sulfonamides should not be given ultraviolet therapy because of the danger of photosensitivity If ambulatory they should be cautioned against prolonged exposure to sunlight

ANTIBIOTIC AGENTS

The most startling paradox of modern medicine is the demonstration that potent antibacterial substances can be isolated and utilized success fully in the treatment of the infectious diseases During the past few years a score of such agents have been derived from soil bacteria fungi actino mycetes and other miscellaneous sources (Table 13 Page 103)

Nature of Antibiotic Agents

Antibiotic agents are natural products of bacteria fungi actinomycetes algae vegetable life and animal tissues and secretions They serve the essential function of adapting a particular organism to the complexities of its environment The great majority of bacteria for example carry out their natural activity in mixed populations This may be illustrated by the microbe population of the soil which includes thousands of species of bac teria hundreds of genera of fungi actinomyces and algae numerous families of protozoa nematodes and other worms and insects (Waksman) In this microbic world some organisms are concerned with highly specific functions such as nitrogen fixation and the production of nitrites from ammonia Many of these processes take place in chain line reactions in which one organism acts on the products of another The chemical versa tility of the bacterial world has led to the assertion that a micro organism could be found to accomplish any given chemical reaction Dubos demon strated this principle when he isolated from soil bacteria an enzyme capable of hydrolyzing the specific polysaccharide of the capsule of Type III pneumococcus

Studies of mixed bacterial population reveal that micro organisms assist one another and also compete with one another They produce both useful and injurious substances Antibacterial substances may be produced in

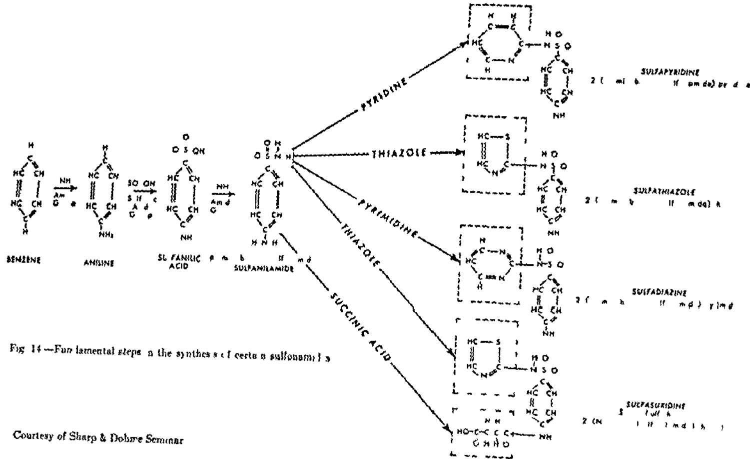


Fig 14 —Fundamental steps in the synthesis of certain sulfonamides

Courtesy of Sharp & Dohme Seminar

in general but it exerts a particularly powerful inhibitory effect against those which decolorize by the gram stain

Preparations—Streptomycin formerly available only for experimental purposes now has been released for clinical use by the National Research Council It is dispensed in ampules which contain the powder in a strength equivalent to 100 000 or 1 000 000 units equivalent respectively to 0 1 G or 1 0 G units *The material is stable and is readily soluble in physiologic* saline solution or in distilled water

Absorption and Excretion—Streptomycin may be administered topically orally intravenously intramuscularly subcutaneously intrathecally intra pleurally or endoscopically by means of a nebulizer When given by mouth streptomycin defies absorption and acts almost wholly on the intestinal content producing an antibacterial effect that should prove of great value in the treatment of enteric infections and in the surgery of the hollow bowel Orally administered streptomycin does not produce significant con centrations in the serum or body fluids and very little is excreted in the urine

Given parenterally streptomycin is readily absorbed and reaches the general circulation so that effectual concentrations are maintained for a period of three hours A significant antibacterial titer may exist for as long as six hours *The drug is distributed through most body fluids* including blood urine ascitic fluid pleural fluid the aqueous the vitreous amniotic fluid the fetal circulation and bile Small concentrations appear in the spinal fluid in the normal individual and large amounts are demonstrable intra thecally in the presence of a meningitis Ideally streptomycin should be given by continuous intravenous drip However for practical purposes as in the case of penicillin repeated intramuscular introduction is the method of choice

Streptomycin is excreted in large concentration by the kidneys so that it has great value in the management of urinary sepsis It is excreted and concentrated in the bile indicating its efficacy in biliary infections The small quantities that diffuse into the cerebrospinal fluid indicate the wisdom of supplementing intramuscular injection in meningitis with intra thecal administration using as much as 100,000 units in 10 cc of *saline* solution

Antibiotic Activity—The antibiotic activity of streptomycin is indicated in detail in the chart which deals with the therapeutics of penicillin and streptomycin (p 111) In general however it may be stated that those organisms which exhibit greatest sensitivity to streptomycin include *E typhosa* salmonellae (paratyphoid) shigellae (dysentery) *E coli V comma* (cholera) *M tuberculosis H influenzae* (meningitis) *Br meliten sis P pestis* (plague) *P tularensis* (tularemia) *Klebsiella* (mucosus cap sulatus of Friedlander) *Pseudomonas aeruginosa* (pyocyaneus) *B subtilis Proteus vulgaris Aerobacter aerogenes* and spirochetes including both trepo nemas (as in syphilis) and borrelia leptospira and spirilla

There are no demonstrable antagonisms between streptomycin and sulfonamides or penicillin, or between either of the latter and streptomycin The antibiotics may be given separately or together using any two or all three noting extreme precautions only when sulfonamides are included in the treatment schedule

Pharmacology

The sulfonamide drugs function within and without the body by interference with the proper functioning of certain enzyme systems that are essential to the multiplication or survival of sensitive bacteria The micro organisms are not killed by the drug unless very high concentrations are used with lesser amounts a bacteriostatic effect is noted and the bacteria are capable of renewed multiplication when removed from the influence of the drug In the tissues of the body a host effect is initiated or accelerated and the bacteriostatic action enables the normal defenses of immunity to destroy pathogens by the processes of phagocytosis and lysis Thus this manifestation of anti infective therapy requires the concerted participation of chemotherapeutic agent and the tissues of the host

The behavior of the sulfonamides to *para aminobenzoic acid* somewhat clarifies the mechanism of the action of the sulfonamide drugs Para aminobenzoic acid is a simple organic chemical isolated from yeast it is widely distributed throughout nature and acts as a growth factor for bacteria it is capable of neutralizing relatively large amounts of the sulfonamide compounds both in the test tube and in the body The antagonism between the two substances suggests that the anti infective agents are not truly lethal for invading bacteria but that through interference with bacterial multiplication and bacterial growth they literally starve the pathogenic organism to death

Therapeutics

The clinical evaluation of sulfonamide drugs as anti infective agents requires consideration as an isolated problem and also in comparative relationship to the potentialities of other remedial agents Exclusive of penicillin and streptomycin the sulfonamides constitute the most potent weapons that the clinician ever possessed in the treatment of infection They may be used topically or systemically and for prophylactic or curative action It is one of the major tragedies of medicine that sulfanilamide synthesized in 1908 (Gelmo) remained unrecognized for its anti infective action until 1935 (Domagk) and that widespread use of this remarkable agency was delayed until almost thirty years later Scarcely were physicians thoroughly familiar with its miraculous effects when the Floreys in 1940 revealed the even more remarkable anti bacterial properties of penicillin whose efficacy had been discovered by Fleming eleven years earlier in laboratory investigations

The comparative value of penicillin and the sulfonamides is the subject of later discussion (p 115) For present purposes the therapeutic indications are listed in reference to the nature of the bacterial invader and if that information is lacking the site or variety of the tissue response The preparation may be given systemically or by topical application it may be intended for prophylactic or curative purpose

THERAPEUTIC ACTIVITY OF THE SULFONAMIDES ON VARIOUS INVADING ORGANISMS

St phylococcus (p 154)

Soluble sulfonamides exert a powerful prophylactic and curative effect resistant strains may be encountered, high concentrations are required over prolonged periods of time

pyoderms purulent maxillary sinusitis osteomyelitis empyema and cystitis The practitioner is warned against parenteral administration Instillations into the conjunctival sac may be attempted in the treatment of pneumococcal conjunctivitis blepharitis epidemic kerato conjunctivitis and dacryocystitis

Penicillin

Penicillin a derivative of the *Penicillium notatum* is the most promising anti infective agent derived from micro organisms It is an extremely potent antibacterial substance both in vitro and in vivo, its pyrogen free sodium salt is practically devoid of serious toxicity to man

Source and Isolation —Penicillin is obtained by growing a suitable strain of *Penicillium notatum* at room temperature for eight days in a synthetic medium (Czapek Dox) The active principle is isolated by acidification and salt saturation of the culture fluid followed by extraction with chloroform and other organic solvents at various *p*H levels It has been obtained as a free acid and as the more stable *sodium calcium potassium* barium and ammonium salts The yield is small and only 1 gm of concentrated material is derived from 100 liters of culture medium

Chemical and Physical Properties —Penicillin has been obtained in crystal line form The free acid which is extremely unstable due to the presence of free carboxyl groups is believed to have the probable formula of $C_{14}H_{19}NO_6$ or $C_{14}H_7NO_5H_2O$ Stability may be increased by the formation of salts and by esterification The aliphatic methyl ethyl and n butyl esters are apparently stable They are inactive *in vitro* but active *in vivo* they are not destroyed by gastric juice and may be made available for oral use

The stability of the different compounds varies The *free acid* is very unstable and quickly deteriorates at room temperature the pyrogen free *sodium salt* which is used therapeutically, is more stable and remains active at room temperature for several hours It is a hygroscopic yellow powder The *calcium salt* is non hygroscopic and apparently more stable at room temperature than the other available preparations Sodium penicillin preparations for therapeutic use should be stored at a temperature of 4°C in sealed ampoules In this manner it loses about 10 per cent of its potency in three months In solution earlier preparations reveal a sharp drop in *potency after twenty four hours even though refrigerated* With purification and improvement in manufacture however more stable solutions are available which retain their properties even at room temperature for four to seven days

The free acid and the various salts are very soluble large quantities of active material may be dissolved in small amounts of distilled water isotonic sodium chloride or 5 per cent glucose These solutions are a pale yellow Deeply colored penicillin which contains an insoluble residue and which foams on preparation is apt to cause untoward reaction

Biological Standardization —Penicillin is an impure compound whose potency varies It is assayed and dispensed according to units rather than by weight The Oxford or Florey unit is that amount which when dissolved in 1 cc of water gives the same inhibition of a standard bacterial culture as a unit of a stable standard penicillin similarly dissolved

ever have been reported in smallpox trachoma inclusion blennorrhea epidemic keratoconjunctivitis and lymphopathia venereum

Fungus Infections (p 189)
Actinomycosis responds favorably to sulfonamide drugs but otherwise systemic fungus infections are unaffected

Protozoa (p 506)
Plasmodia amebae leishmania and trypanosomes are sulfonamide resistant

Helminths (p 537)
The helminthes are sulfonamide-resistant

Therapeutic Indications According to the Site or Variety of the Tissue Response—When the practitioner is unable to obtain bacteriologic data the sulfonamide drugs may be administered on the basis of the site or variety of the local inflammatory process The use of the chemotherapeutic agent merits consideration in abscess appendicitis arthritis bacteremia bites burns carbuncles cellulitis colitis conjunctivitis empyema endocarditis endocervicitis endometritis enteritis erysipelas fractures furuncles gun shot wounds impetigo lymphadenitis lymphangitis mastitis mastoiditis meningitis osteomyelitis otitis media pelvic peritonitis perforation of the hollow bowel peritonitis peritonsillar abscess pneumonia puerperal sepsis preliminary to surgical procedures in which there may be soiling of the thoracic or peritoneal cavities prostatitis salpingitis septicemia sinusitis sycosis tissue injuries tonsillitis urethritis urinary sepsis and vaginitis

Fastness —The condition of fastness exists when certain susceptible organisms notably staphylococci gonococci and streptococci no longer exhibit bacteriostatic or bactericidal effects in the presence of adequate concentrations of sulfonamide drug In certain instances it appears that the particular organism possesses a *natural immunity* to sulfonamide therapy in other circumstances there is a suggestion that drug fastness is acquired One way or another the clinician does not encounter the favorable effect he has reason to anticipate and the experience must be classified as a treatment failure Sulfonamide fast organisms may be susceptible to penicillin as best exemplified in *gonorrhea* contrariwise an occasional organism is encountered which is penicillin fast but sensitive to sulfonamide which then exhibits a specific anti infective action where the penicillin has failed

Masking —In the treatment of the suppurative processes the sulfonamide drug may reveal a masking effect in that the patient seems to be progressing favorably while there is extensive necrosis and widespread destruction of tissue This is particularly illustrated in *middle ear infections* the patient becomes symptom free and afebrile whilst the complications of mastoiditis and sinus thrombosis may be silently advancing On this account conditions notoriously associated with suppuration require the closest clinical observation In the management of an ear infection for example if sulfonamide therapy is inaugurated preliminary and serial roentgenography of the mastoid cells should be practiced at three or four day intervals for the early detection of masked suppuration and bone destruction (p 2146)

Sulfonamide Streptomycin and Penicillin

There are no demonstrable antagonisms between sulfonamide streptomycin and penicillin More likely these potent antibiotic agents potentiate

manufacturer's direction when the oil wax mixture is used The solution must be thoroughly fluidified by heat the syringe must be scrupulously dry and the needle must be 18 gauge or wider

Absorption and Excretion —Penicillin is absorbed by almost any route and is rapidly excreted in the urine Optimum concentrations are obtained by continuous intravenous administration using the drip method (p 3775) A total daily dose dissolved in 3000 cc of physiologic saline solution and run at a rate of 3 cc per minute may deliver as little as 200 000 and as much as



Fig 15A —Pulmonary abscess in upper pulmonary field before treatment with penicillin

2 000 000 units per 24 hours With almost equal efficacy 10 000 to 200 000 units of penicillin may be injected intramuscularly at intervals of 2 or 3 hours using no greater quantity than 2 cc of diluent For more protracted effect a single injection of 300 000 units in 1 cc of a mixture of oil and wax (Romansky) may maintain a satisfactory level for six to twelve hours In constant effects with an efficiency that averages only 20 per cent result from the oral use of buffered tablets capsules in vegetable oil and suspensions in aluminum hydroxide gel

* Herrell Penicillin and Other Antibiotic Agents

but in rare instances it may reach 106° *Chills malaise headache* and *joint pain* may also be present and the clinical picture then is indistinguishable from serum sickness

Drug fever is an indication for cessation of sulfonamide treatment subsequent repetition of the drug is likely to cause a febrile recurrence

Dermatitis —Eruptions are produced by all the sulfonamide drugs The rash may be *purpuric scarlatiniform morbilliform* or *urticarial* In rare instances an acute *exfoliative dermatitis* or a *pemphigus like eruption* may lead to a fatal outcome Sulfonamide rashes are often associated with *fever* and *intense itching* They may be local or general in distribution and they tend to occur on the face trunk and extremities The skin lesions produced by sulfathiazole are often nodular and resemble an *erythema nodosum* (p 3377) See Fig 15

With the toxic dermatosis a *condition* resembling *pink eye* characterized by scleral and conjunctival injection may be seen from the fifth to ninth day

Sensitization —If a patient develops a drug fever or a rash following the first administration of a sulfonamide the reaction is apt to recur with the second administration of the drug If a second course of sulfonamide is needed another product should be used in a probatory manner or penicillin should be substituted

Blood and Blood Forming Organs —The sulfonamides are capable of damaging the peripheral blood cells and the bone marrow This property is common to the entire group of aniline derivatives and is seen with arsphenamine aminopyrine and other drugs having this basic structure

Cyanosis is most frequent with sulfanilamide but is much less common with the other sulfonamides particularly sulfadiazine Unless it is intense it may be disregarded The origin of the blue color has not been definitely established but most available evidence indicates that methemoglobinemia is involved in its production The use of methylene blue has been recommended to combat methemoglobin formation with intense cyanosis but a simpler procedure is to substitute sulfadiazine

Long continued administration of sulfonamide particularly sulfanilamide and sulfapyridine may produce a moderate *hyperchromic macrocytic anemia* The hemoglobin drop to 50 or 60 per cent and may necessitate blood transfusion The anemia is associated with a *reticulocytosis* and *urobilinuria* suggesting a hemolytic process the bone marrow shows evidence of hyperplasia *Promin* produces varying degrees of hemolytic anemia with some regularity

A dramatic complication of sulfonamide therapy is the development of an *acute hemolytic anemia* After the first few doses the hemoglobin may drop as much as 70 per cent in twenty four hours The patient complains of chills and generalized muscle pains the sclerae are icteric and the liver may be enlarged and tender there is a spiking fever the urine has a dark wine to brown color due to the presence of free hemoglobin A second course of sulfonamide is likely to cause a recurrence of acute hemolytic anemia which is treated by discontinuance of the drug forced fluids large doses of sodium bicarbonate to prevent precipitation of hemoglobin in the renal tubules and blood transfusions This reaction is most common after sulfanilamide and is extremely rare in patients receiving sulfadiazine

latter is useful as a supplementary measure in private practice when the physician is burdened with the entire care of his patient and cannot return at frequent intervals for repeated intramuscular injections As an alternative oral tablets may be employed though the wastage with them is great the cost is excessive and the efficacy by no means comparable to parenteral methods

In an acute infection failure should not be acknowledged until the lapse of three to five days at the end of which time the patient will have received no fewer than 30 injections and no less than one or two million units In a chronic infection the duration and unitage should be doubled or trebled before calling quits

Unlike streptomycin penicillin is not excreted in the feces even when given by mouth The main excretory channels are the kidneys so that the antibiotic effect is valuable in the treatment of urinary sepsis Penicillin is excreted and concentrated to some degree in the bile indicating its value in the biliary infections It passes the placental barrier in pregnancy and may be utilized for the treatment of the fetus particularly in the control of neo natal syphilis Insufficient quantities of penicillin are excreted into the cerebrospinal fluid and into abscess cavities As a result it is wise to supplement parenteral injections of penicillin with local instillations into an empyema thoracis or into the cerebrospinal fluid in dealing respectively with pleural suppuration or meningitis caused by a penicillin sensitive organism

Mechanism of Action —The behavior of penicillin in the body is unique It is unlike that of any other known chemotherapeutic agent with the pos sible exception of streptomycin In all likelihood it owes its potency to inter ference with the metabolic activity of susceptible species of bacteria Its efficacy is not inhibited by pus blood serum or para aminobenzoic acid but it may be weakened by bacterial products

Antibiotic Activity —Penicillin may be bacteriostatic bacteriolytic or bactericidal depending on experimental conditions In actively growing cul tures it causes decrease in the numbers of organisms In static cultures it only prevents multiplication and the tissues of the body then destroy the non reproductive forms of the bacteria It does not impede leukocyte action It is many times more powerful than any of the sulfonamides and exhibits an elective effect upon specific microbic invaders

In general the penicillin sensitive strains of bacterial life include staph ylococci hemolytic streptococci pneumococci meningococci gonococci *B anthracis* clostridia (tetanus and gas gangrene) *C diphtheriae Cl botu linum* spirochetes including *Tr pallidum* of syphilis and actinomyces

Not all strains of penicillin sensitive organisms are equally affected *Staphylococcus aureus* may develop a high degree of resistance and the *Staphylococcus albus* may be completely unaffected There is some evi dence that resistant staphylococcic strains elaborate a penicillinase capa ble of destroying the antibiotic action

Therapeutics of Penicillin and Streptomycin

It has seemed advisable to combine the discussion of the therapeutics of penicillin with that of streptomycin It is difficult to speak of these anti biotics without indulging in superlatives Their coverage is wide toxicity is negligible fastness is unusual patient sensitivity is rare the available preparations are stable and the technics of injection are simplicity itself

TABLE 11.—THE COMPARATIVE EFFICACY OF THE SOLUBLE SULFONAMIDES

Observ t	Sulfanil m d	Sulf pyrid e	Sulf thiazol	Sulfadiaz e	Sulf m razin
P ce t of absorpti from bow l	95-100	40-70	80-90	80-90	80-90
H rs f mplet bsorptio	4	5-6	3 6	3-6	3 6
P ce t i C S F	75-80	60-80	10²	50-75	0-66
Gen ral tiss d trib t	Equal	Equal except in C S F	Eq l but ery l w C S F	Eq l but in C S F co ce tratio ly ⅔ of blood	Equal b t C S F co cen trat ly ⅔ f blood
Blood co tratio from therape t doses (m lligrams per t)	7 10	4-6	3-6 but f lls rapidly	8-12	9-13
M inte ce f blood co ce trati	Pr l ged	Prol ged	R p d f ll	Prol nged	Very prol ged
I ce t f blood acetyl tio	10- 0	50-7	10-30	1 0	8-15
1 t ret in rin	90⁴	40-60	80-90⁴	70-90	70-90
P ce t ac tyl tio n	5-50	50-80	10-30⁴	5-35	30-60
S l l t f ac tylate uri (m ll gram pe t)	5 34	16	6	15	8
T d y to rol thiasis	Sl ght	Gre t	Great	Slight	Sl ght
N use and m t g	10-20	40-55	3-40	9	4 7
H ad h d d ess	5-10	0 3-5	0	0 5	1
T d rm toses	5	4-5	8-10	3	3-6
J i	O l	R re	Rare	Rar	Rare
A m (pe ent)	1	2 3	R re	Rare	R re
Leukopen a d gra l pen	Occasi nal	Occas l	Rare	Rare	Rare
Hem t d l gun	Rare	8 per cent	2 5 pe t	1 per ent	Ra
Drug fever (r ce t)	10	5	5-6	1	3-6
St phyloc ccal ffect	N t used	N t used	Thir l h ce	First h ce	e d h
Strep toc l ff ct	Third hoi	F th h	Fifth h	F rst h	Sec d h
P umococ l ff t	N t d	Fourth h ce	Th rd h	First h	Sec d h
Men gococ l ff t	N t used	Fourth h	Th d h	First ho	Seco d h
G ococcal eff t	N t used	Fourth h	Th rd h ce	First h	Se d h

NOTES T 11

Observ po s d rregul bsorpt f *ulf pyrid*
Observ low t t f *sulf thiaz le* cerebrosp l fl d d b l ty with *sulf mer n*
Observ rel ti ly l w blood co entratio with *sulfathiazole* d pid f ll so th t larg doses m t be d t m re f q t terv l
Obse h her trat with *ulf mer zi* d l w f ll so th t sm ll doses be used t greate terv l
Observ h gh bl od acetyl t pe tag with *ulf pyrid* so th t m h f th ffect f th d g act ed bsc l w pe entag f blood cetyl tio with *ulf diazi* so th t th re bu d f f e sulf m d f t feet tivity
N te p l d h gh ur ry ex tions of *lf ilam d* d *ulf thia ole* so th t these preparations best f urinary f tio
Observ l gh cetyl t on f *ulf pyr d* rine f ing th form t f rystals d st es
Observ h gh q t ty f *acetyl t* th uri w th *sulfathia ole though perce tag* low th ls f ts th f rm t rystal ls d tones
N te th gr t sol b l ty of *sulf lamid acetylat* th n so th t ry tals d t tend to f rm
N te l b l t f th *ulfath ol* d *sulf pyrid acet late* f ring th f rm t f rystals d t es
N te th part cul ly high d f se d omitu g with *sulf pyrid* d *ulf th le* greatl add g t th diffi lt es nd d scomf rts f admi tratio
N te h gh idence f head h d ess d ther eurol g cal m fest tions w th *sulf lam d* thus ld g to p tient d scomf rt
N t h h d f t derm toses with *sulf th ole* so th t th p p t h uld be used ti ly f t ll n tient k ow to h m lt pl sen t vit es th ll g co t t t on
14 N t h gher dence f j d d em with *s lf lam d*
N te l t ly h gher den f emia with *lf pyrid*
N te p rt cularly h gh d f *hem t* with *sulf pyrid*
N t p rtic la ly high mud f drug fev with *sulf lam de, sulfath azol* *sulf mer zine*

Toxicity—A remarkable property of penicillin is its lack of serious toxicity Impure batches of earlier preparations caused a variety of un toward reactions due to pyrogens The highly purified preparations pres ently available appear to be almost inert so far as toxicology is concerned An occasional patient develops urticaria with slight elevation of temperature perhaps some generalized abdominal cramps or diarrhea At times a moder ate elevation of non protein nitrogen has been observed as the result of the inhibition of the urease enzyme by penicillin

Indications for Antibiotic Therapy Other than the Nature of the Invading Micro Organism

The exigencies of clinical practice may demand inauguration of anti infective therapy without exact knowledge of the nature of the bacterial invader This principle previously discussed in relation to sulfonamide holds with even greater potency in the cases of streptomycin and penicillin since these latter are relatively innocuous preparations so far as the tissues of the host are concerned

The indications for streptomycin based on the site of the inflammatory process have elsewhere been enumerated (p 105) Penicillin therapy merits consideration when the local lesion is an abscess an appendicitis an arthritis a bacteremia a bite a burn a carbuncle a cellulitis a conjuncti vitis an empyema an endocarditis an endocervicitis an endometritis an erysipelas a compounded fracture a furuncle a gun shot wound an impetigo a lymphangitis a mastitis a mastoiditis a meningitis an osteo myelitis an otitis media a pelvic peritonitis a generalized peritonitis a peritonsillar abscess a pneumonia a puerperal sepsis a proctitis a salpin gitis a septicemia an accessory nasal sinusitis a sycosis a tonsillitis a urethritis a urinary sepsis or a vaginitis

Prophylactic therapy with penicillin is indicated in exposure to penicil lin sensitive organisms as in an epidemic of scarlet fever and in surgery when contamination with a penicillin sensitive organism may be expected as in procedures involving the oropharynx pleura peritoneum bones or joints

Penicillin and Surgery—Despite unlimited enthusiasm for penicillin therapy the practitioner must bear in mind that the remedy cannot drain pockets of pus nor eliminate the necessity for surgical intervention in vein infections The surgical consultant should have the opportunity of observ ing the penicillin treated patient in order to institute necessary drainage and ligate or excise infected vein segments when indicated

Penicillin and Serum—Penicillin is an anti infective but not an antitoxic agent In consequence there are many clinical situations in which the anti biotic substance must be given in conjunction with antitoxin Illustrative of these are toxemias associated with diphtheria botulism anthrax tetanus and gas gangrene In dealing with these situations penicillin is directed toward destruction of sensitive bacteria but it cannot neutralize the already absorbed toxin antitoxin has no antibacterial action but may counteract poisonous effects of bacterial products

Penicillin and Sulfonamide—Previous reference has been made (p 104) to the fact that sulfonamide and penicillin are not antagonistic they may in fact potentiate one another and be synergistic Their mechanisms of

Ointment

Use 5 per cent sulfanilamide sulfathiazole or sulfadiazine in greaseless base (aquaphor) For higher local concentrations use sodium salts

Oral Adm nistrat on

Initial Dose

ADULTS

To obtain blood concentration of 5–10 mg per cent give init al dose of 4–6 gm of sulfadiazine sulfamerazine or sulfathiazole At same time give heaping teaspoonful of bicarbonate of soda and 2 glasses of flu d

To obtain blood concentration of 10–15 mg give 6–8 gm with 2 teaspoonfuls of bicarbonate of soda and 2 glasses of fluid

CHILDREN

Give 0 15 gm per Kg or 1 gm for each 15 pounds up to total dose of 3 gm

Subsequent Doses

ADULTS

One gm every 4 hours with bicarbonate and water

CHILDREN

Give 0.5 to 1 gm every 4 to 6 hours as indicated

R ctal Adm strat on

Not advised

Subcutaneous Administration

Use 1 per cent sulfanilamide in saline or ⅙ molar sodium lactate Give 10 cc per Kg or 100 cc for each 22 pounds Use sodium sulfadiazine or sulfathiazole as in intravenous

I t amuscular Adm n strat on

Not advised

I t a e s Adm strat on

Use 5 per cent sodium salt of sulfad azine sulfamerazine or sulfathiazole Give 0 06 to 0 1 gm per Kg or 12 to 20 cc for each 22 pounds

Also may use 25 per cent sod um salts giving ⅕ of above dose by *very slow* injection

Topical Use—The topical use of the sulfonamides has been enthusiastically exploited without due consideration of limitations and dangers The hope and expectation of local bacteriostasis are not justified by theoretical or practical consideration The sulfonamides are not directly lethal to bacteria as is iodine They require tissue participation for their bacteriostatic and bacteriolytic proclivities and their therapeutic activity is lessened and almost nullified by the presence of pus blood dead bacteria and procaine an ester of para aminobenzoic acid

In addition to distinctly limited local parasitropism topical applications of sulfonamide possess demonstrable and theoretical hazards for the host They may cause the same toxicity as systemic doses they delay healing and they may produce sensitivity so that systemic employment at a future time may be precluded

The tempered attitude toward the topical use of sulfonamides has been best summarized by Darke (J.A.M.A *124* 403 (May) 1944) in the following statements Because sensitivity may preclude the use of the drug in

of gram negative and gram positive organisms is accomplished at no more risk than is engendered by the administration of either of the antibiotics separately If the patient is not desperately ill, treatment may be initiated with either one, reserving the other for treatment failure Finally penicillin and streptomycin may be given concurrently with sulfonamide In this last instance however the hazards incidental to sulfonamide therapy are introduced and patient management is complicated by the factors elsewhere enumerated (p 101)

'Probatory' and 'Desperation Antibiotic Therapy

Aside from the specific indications for the uses of penicillin and streptomycin in the treatment of infections with known sensitive strains we favor the administration of these remedies in the management of any moderately severe or progressive infection in which the usefulness of the products has not yet been completely defined Because of the innocuousness of penicillin and streptomycin we shall practice *probatory chemotherapy* in all severe or protracted infectious states including those in which reports indicate that the products are of dubious or uncertain value We shall continue to give these drugs until they have proved useless rather than wait at the sacrifice of human life until long term statistics justify their administration Our attitude is much like that of the American Courts which believe that a man is innocent until proved guilty

Beyond probatory chemotherapy we shall also practice *desperation chemotherapy* By this we mean that we shall give penicillin and streptomycin in full and prolonged dosage in the treatment of infections in which these remedies are reputed to be useless provided that the prognosis is unfavorable the course of the disease severe or its progress protracted or unsatisfactory Undoubtedly we shall waste much good penicillin and streptomycin between probatory and desperation anti infective therapy but we have no doubt that we shall occasionally witness a small miracle whether or not the successful issue is capable of explanation at the termination of the clinical experiment

In anticipation of the criticism of academicians who will not accept the principles of probatory and desperation anti infective therapy with penicillin and streptomycin we advance the following arguments to sustain our position

1 Test tube pharmacology is not human pharmacology Organisms destroyed by anti infective agents in the body may survive in solutions of the same substance in the test tube This is true of spirochetes in a solution of arsphenamine of susceptible cocci in a solution of sulfonamide and of plasmodia in a solution of quinine

2 Animal pharmacology is not human pharmacology Experimental animal infection differs biologically from spontaneous human infection the responses of the artificially infected animal are not necessarily the responses of the spontaneously infected human being Experimental rabbit syphilis for example can be cured with a single intravenous injection of almost any arsenical but certainly not even the most enthusiastic syphilologist would claim comparable results in the human Were the principles of animal pharmacology followed for example in spirochetal invasions the conquest of syphilis by penicillin would have been delayed even further by those guided by rabbit medicine

Effects on Bowel —The insoluble sulfonamides are absorbed to a negligible degree and exert their principal action on the fecal column The coliform flora is markedly decreased the numbers of the clostridia are lessened but the *streptococcus faecalis* is not inhibited Enemas irrigations mineral oil frequent evacuations or inspissation of stool interfere with drug action The drug effect is noted grossly after one to seven days the feces becomes *semifluid small in bulk gelatinous and odorless* The coli count per gm of wet stool falls from 10 000 000 to less than 1 000 At this time the dose of the preparation may be decreased by giving the drug at 6 or 8 hour intervals

Determination of Sulfonamide Concentrations in Body Fluids

The determination of the concentration of sulfonamide in the blood (p 3717) is desirable in the treatment of every acutely ill patient Since there are individual variations in excretion and absorption the blood level is a guide to inadequate dosage and it may reflect a tendency for the drug to remain in the body as a result of impaired excretion

TABLE 12 —THE INSOLUBLE SULFONAMIDES

	Sulfaguanidine	Sulfasuxidine	Sulfathalidine
Initial dose in mg per Kg	0	100	40
Total initial dose for 10 Kg (22 lbs)	0 5 gm (1 tablet)	1 25 gm (2½ tablets)	0 5 (1 tablet)
Total initial dose for 70 Kg (154 lbs)	3 5 gm (7 tablets)	7 gm † (14 tablets)	2 8 gm (6 tablets)
Daily maintenance in mg per Kg (6 doses)	300	250	125 to 2 0
Total single daily dose for 10 Kg (22 lbs)	0 5 gm (1 tablet)	0 5 gm (1 tablet)	0 5 gm (1 tablet)
Total single daily dose for 70 Kg (154 lbs)	3 5 gm (7 tablets)	3 0 gm (6 tablets)	2 8 to 5 6 gm (6 to 12 tablets)
Toxicity	Most	Intermediate	Least

Tablets of 0 5 gm (7½ grains)
† Observe unwieldy initial dose

The chemical methods for the determination of sulfonamides in blood and urine are elsewhere described (pp 3690 3717)

Practical Rules of Management of Patients Receiving Sulfonamides

The average patient receiving sulfonamide therapy should be subjected to a strict medical regimen to facilitate the most efficient use of these compounds and to protect against toxic manifestations The following rules are suggested

1 Ambulatory patients must be seen once a day The seriously ill should be seen twice daily preferably in the hospital
2 A history of previous sensitivity to a sulfonamide should be sought

of gram negative and gram positive organisms is accomplished at no more risk than is engendered by the administration of either of the antibiotics separately If the patient is not desperately ill treatment may be initiated with either one reserving the other for treatment failure Finally penicillin and streptomycin may be given concurrently with sulfonamide In this last instance, however, the hazards incidental to sulfonamide therapy are introduced and patient management is complicated by the factors elsewhere enumerated (p 101)

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artificial media and extracted in highly potent and relatively pure form *some act on many and others on only a few* micro organisms through influences on cell division cell respiration and tissue metabolism

Specific Antibiotic Substances

Innumerable antibiotic substances must exist in nature The principal preparations which have been isolated and studied include the group in Table 13

TABLE 13 —THE ANTIBIOTICS

Antibiotic	Comment
ACTINOMYCETIN	Effective against gram neg and gram pos organisms
ACTINOMYCIN A AND B	Effective against gram pos organisms Toxic
ALLICIN	From garlic Equally effective against gram neg and *gram pos organisms*
BACITRACIN	See p 115
CANAVALIN	From soy or jack beans Effective against gram neg and gram pos organisms with co-enzyme
CHLORELLIN	From algae Inhibits gram pos cocci and *E coli*
CITRININ	From penicillium Effective against gram pos organisms but toxic
CLAVACIN (*Patulin Claviform n Clavatin*)	*Ineffectual in common cold* despite early favorable reports Toxic
FLAVICIN AND FLAVACIDIN	From aspergillus Resemble penicillin Low toxicity
FUMIGACIN (Helvolic Acid)	Effective but hepatotoxic
FUMIGATIN	Effective against gram pos but toxic
GIGANTIC ACID	Resembles penicillin
GLIOTOXIN	Effective but toxic
GRAMICIDIN	See Tyrothricin (p 105)
LYSOZYME	Enzyme present in body fluids such as nasal mucus tears sputum blood et Inert in clinical therapy
PENICILLIC ACID	Effective against gram neg and gram pos organisms
PENICILLIN	See p 106
PYOCYANASE AND PYOCYANINE	From pseudomonas Effective but toxic
STREPTOTHRICIN	Effective against gram neg and gram pos organisms but toxic Apply locally as tyrothricin (p 105)
STREPTOMYCIN	See p 103
TYROTHRICIN	See p 105

This table partially indicates the complexity of the problem of presenting the clinical therapeutics of antibiotic substances The usefulness of streptomycin tyrothricin and penicillin are discussed in the paragraphs which follow immediately

Streptomycin

Streptomycin is a powerful antibiotic preparation that is derived from *Actinomyces griseus* It can be produced on nutrient glucose broth with the aid of a growth promoting substance Chemically it is an organic base that is soluble in water and in acid solutions but not in ether or chloroform It is thermo stable and sensitive to acid It is a potent agent against bacteria

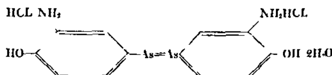
THE ARSENICALS

The discovery of arsphenamine by Ehrlich after an exhaustive search for an effective remedy for syphilis laid the foundation of the modern science of chemotherapy Since then many organic arsenicals have been synthesized to provide more effective and less toxic chemotherapeusis for *syphilis* and allied *trepanematoses trypanosomiasis* and *amebiasis*

Organic Arsenicals —Organic arsenicals may be *trivalent* or *pentavalent* the former are used in the treatment of *syphilis* the pentavalent arsenicals possess limited antisyphilitic value but are extremely useful in *trypanosomiasis* (p 531) and *amebiasis* Acetarsone and carbarsone pentavalent arsenicals effective in amebiasis are discussed in the section devoted to amebacides (p 527)

Trivalent Organic Arsenicals—The various arsphenamines are complex organic compounds containing two atoms of trivalent arsenic joined by a double bond The structural formula of *arsphenamine U.S.P* the parent substance appears as follows

ARSPHENAMINE—Diaminodihydroxyarsenobenzene Dihydrochloride—Contains not less than 30 per cent and not more than 32 per cent of arsenic (As) and complies with the requirements of the National Institute of Health United States Public Health Service *U S P*



Arsphenamine U S P is a complex organic arsenical which was originally known as salvarsan (606) It is a light yellow powder The free base is insoluble and unstable hence the drug is dispensed as the soluble dihydrochloric acid salt It is carefully packed in vacuum sealed ampoules which must be stored in a cool place On exposure to air the compound becomes darker and toxic Arsphenamine should be used within 5 years of manufacture

Before arsphenamine can be administered the acid salt must be converted into a *disodium salt* by the addition of alkali For intravenous use the preferred route of administration N N R recommends the following procedure

The ampoule containing the drug is immersed in alcohol in order to be sure that a cracked tube is not being used then the tube is carefully wiped off the neck filed across and broken off and the contents sprinkled on sterile distilled water (10 cc for each 0 1 gm of the drug used) contained in a sterile Erlenmeyer flask The drug is allowed to dissolve with little or no agitation Normal sodium hydroxide is then added to the solution using 0 85 cc to every 0 1 gm of the drug Thus 0 6 gm of the drug would require 5 1 cc of normal alkali A precipitate of the base is first formed which after the contents are carefully agitated is again brought into solution the fluid being strongly alkaline The alkalinized solution is filtered through sterile gauze 4 ply and the filtrate is diluted with sterile distilled water to make 25 cc for each 0 1 gm of the drug It should stand 30 minutes before using At least one minute should be allowed for each 25 cc of the solution to flow into the vein using the gravity method The contents of a tube should be used at once after opening and under no circumstances should the contents of a tube damaged in transportation or any remnants of the powder from previously opened tubes be used Solutions that have been exposed to air for more than 30 minutes should not be used because toxic oxidation products are formed The injection should be done carefully with caution to prevent

The indications for antibiotic activity with streptomycin are not limited to definitive recognition of the nature of the invader a condition which prevails also in the practical therapeutics of sulfonamide and penicillin At times the practitioner may find it incumbent upon himself to administer streptomycin merely on the basis of the nature of the inflammatory process with which his patient is afflicted Thus streptomycin appears indicated in enteric infections peritonitis urinary sepsis biliary fevers and conditions which resist treatment with sulfonamides and penicillin When given orally as for enteric fevers and in the preparation of the patient for surgery of the hollow bowel the daily dose may prove to be as great as 2 000 000 to 4 000 000 units Given parenterally as by intramuscular injection 250 000 to 1 000 000 units injected four or five times daily may be required in order to obtain and maintain effectual tissue concentrations Thus it appears that the unitage of streptomycin is in excess of penicillin dosage Because of better maintenance of serum concentrations injections can be given at 4 or 6 hour intervals instead of at 2 or 3 hour intervals as in the case of penicillin

Toxicity —Injections of streptomycin are apt to produce local irritation which may be avoided by the simultaneous use of 1 0 cc of 2 per cent procaine Distant toxic manifestations include occasional nausea or vomiting toxic erythema urticaria transitory arthralgia and myalgia Impurities in the preparation of the antibiotic may result in the production of chilling and fever Renal and hepatic function are not impaired even with massive dosage No serious damage has been observed in the hematopoietic system from large doses given over relatively long periods of time but auditory neuritis may produce tinnitus ataxia and transitory deafness

Tyrothricin

Tyrothricin is a powerful antibacterial agent derived from a number of strains of *B brevis* a soil bacterium It is separable into two distinct fractions *gramicidin* and *tryocidine* Because of marked systemic toxicity the products of tyrothricin have limited applicability since they can only be administered topically

Antibiotic Activity —Tyrothricin is effective against gram positive and gram negative bacteria *Gramicidin* is active against gram positive organisms meningococci and gonococci Its greatest efficacy is evident against the pneumococcus less against streptococci and least against staphylococci Unfortunately gramicidin is partly inhibited by serum peptone and tissue extracts it is ten times more toxic than penicillin and produces extreme hemolysis *Tyrocidine* exhibits bactericidal and bacteriolytic action on gram negative and gram positive organisms Like gramicidin its efficacy is inhibited by serum peptone and tissue extracts so that it is almost inert in the living organism Additionally it is a general protoplasmic poison and produces hemolysis and destruction of leukocytes

Therapeutics —The Council on Pharmacy of the American Medical Association has accepted a commercial preparation of *Tyrothricin N.N.R* The product is marketed in ampoules of 25 mg per cc Each package includes an ampoule containing 49 cc of distilled water so that a dilution can be obtained in which each cc contains 500 micrograms of the preparation Local applications of tyrothricin are useful in the treatment of chronic ulcers of the skin

ing the ampoule the contents are sprinkled on the surface of 5 cc of cool (20–22° C) sterile *distilled water in a small sterile flask* Heating and shaking must be avoided A quantity of cool sterile solution of 0.4 per cent sodium chloride is added so that the final solution will approximate 20 cc of liquid per decigram (0.1 gm) of the drug *The solution must be given promptly and slowly* The solution is relatively non irritating to veins

The average adult dose is 0.1 gm to 0.3 gm (1½–4½ gr) Treatment is started with 0.1 gm (1½ gr) and increased slowly

Sulfarsphenamine N N R is a light yellow powder containing 19 per cent trivalent arsenic It is the most soluble of the compounds and is slightly acid to litmus in aqueous solution It decomposes slowly when solutions are exposed to air for many hours On standing overnight the solution darkens and a precipitate forms

NaOS O CH NH   NH CH –O₂–SONa

HO–   –As—As–   –OH

The ampoule is opened directly after a careful inspection Distilled cool water is added directly to the ampoule in the proportion of 0.3 cc for every 0.1 gm of drug The total volume of solution should be at least 1 cc Solution is prompt and complete There is less local reaction when a minimum of diluent is used

The drug may be given intramuscularly subcutaneously or intravenously The latter route is not recommended because the toxicity is increased by this route For intravenous use the drug should be well diluted the total volume amounting to 5 to 20 cc or more As a rule sulfarsphenamine is given intramuscularly in early congenital syphilis and in patients whose poor veins preclude the intravenous use of arsenicals There is a higher percentage of toxic reactions with this drug than with the other antiluetic arsenicals Consequently it should be used only in rare instances where its administration is obligatory

The average intramuscular dose for adults is 0.5 gm (7½ gr) In infants 10 to 25 mg (1/6 to 3/8 gr) per kg *of body weight* are given intramuscularly Infants are less susceptible to the toxic reactions

Bismarsen (Bismuth Arsphenamine Sulfonate) N N R is a derivative of arsphenamine containing bismuth It contains about 13 per cent trivalent arsenic and 24 per cent bismuth It is a brownish yellow amorphous powder which readily yields a yellow aqueous solution slightly alkaline to litmus

After careful inspection the bismarsen ampoule is opened and 1 cc of cool sterile distilled water for each 0.1 gm of drug is added directly to the ampoule Two to 3 drops of a 2 per cent solution of butyn are added to the solution to allay the slight pain on injection

The drug is given intramuscularly The initial dose is 0.1 gm (1½ gr) and this is followed by injections of 0.2 gm (3 gr) biweekly in courses of 20 doses or more The clinical status of bismarsen remains to be established but it seems therapeutically inferior to other arsphenamines

The activity of penicillin may be determined by serial dilution or plating. By the former technic the unit is that amount of penicillin which when dissolved in 50 cc of a liquid medium will inhibit the growth of a standard inoculum of standard staphylococcus under standard conditions. In the plate method one unit is the amount that produces a zone of inhibition of 24 mm on a plate of nutrient agar seeded with standard staphylococcus.

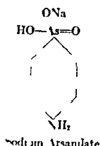
Preparations.—Many preparations of penicillin are commercially available for use by the practitioner. The most important are indicated below

Dental Cones	For topical application (500 units)
Troches and Lozenges	For oropharynx (1000–1500 units)
Powder	For topical application (10 000–50 000 units per vial. Add saline to make solution)
Ointments	For topical or ophthalmic use (1 cc = 1000–1500 units)
Solutions for topical use 1 cc = 500–10 000 units	For application to surfaces, mucous membranes and conjunctiva. For nebulization and aerosolization (p. 2041)
Products for oral ingestion (containing 50 000 units)	Buffered tablets (trisodium citrate). Capsules in vegetable oil. Suspensions in aluminum hydroxide gel
Suppositories	For rectal insertion (10 000–50 000 units)
Solutions in sterile physiological saline with or without 5 per cent dextrose	For repeated intramuscular or intravenous injection (1 cc = 10 000–100 000 units). For continuous intravenous or intramuscular drip infusion (1 cc = 25–250 units). For injection into aqueous, cerebrospinal fluid, empyema cavities, etc.
Suspension in oil and wax (for slow absorption)	One cc = 100 000–300 000 units. Fluidify by heat. Withdraw into dry syringe. Use 18 g. needle

It is our opinion that dosage tables for penicillin call for quantities that are altogether too small. Undoubtedly this tendency goes back to the early days of antibiotic therapy when supplies were inadequate for the great needs. Some of the early disappointments of penicillin therapy can be attributed to small dosage rather than to insensitivity to the therapeutic agency. Thus the original dosages used for gonorrhea and syphilis respectively were 60 000 and 1 200 000 units. Our practice is to use in gonorrhea 500 000 to 1 000 000 units and in syphilis no less than 10 000 000 units. The hazard of toxicity is negligible and the practitioner cannot expose his patient to the risk of failure merely to save material or reduce the numbers of the injections.

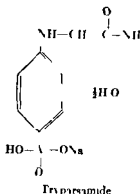
The practitioner under the circumstances that prevail in private practice often is compelled to use several preparations of penicillin in order to achieve and maintain constant and adequate antibiotic levels. There is no difficulty if repeated intramuscular injections can be arranged day and night at two- or three-hour intervals. More often, however, improvisations are required and recourse may be had to supplementary oral dosages or an intramuscular deposit of the oil wax preparation. If dependence is placed on the oral product five times the intramuscular dose should be used at two- or three hour intervals. If the oil and wax mixture is injected 300 000 units are introduced in 1 cc and a satisfactory level may be anticipated for a period of eight to twelve hours. The practitioner is cautioned to follow

Pentavalent Arsenicals—The pentavalent arsenicals are derivatives of arsanilic acid The parent compound is *atoxyl* which has the following structural formula



Sodium Arsanilate

Tryparsamide very similar in chemical structure differs only in the presence of a glycinamide group on the para amino group



Tryparsamide

Tryparsamide (Sodium N phenylglycinamide p arsonate) is a complex organic compound containing 25 per cent arsenic in pentavalent form It is a white stable crystalline substance which is quite soluble in cold water forming a solution which is neutral to litmus The required amount is dissolved in 10 to 20 cc of sterile distilled water and is given intravenously with a syringe It may be given also intramuscularly in 3 cc of water it should never be given by mouth In general the dose of tryparsamide should not exceed 0 04 to 0 05 gm per kilogram of body weight the total dose varying from 1 to 3 gm (15 to 45 gr) for the adult At least one week should elapse between successive injections

The antiluetic value of tryparsamide is limited to the treatment of syphilis of the central nervous system especially general paresis It is most commonly employed after malaria therapy The drug is especially apt to cause a *toxic amblyopia* and its use should be preceded and attended by careful study of the visual and color fields In the presence of visual field contraction its use is contraindicated

Tryparsamide is a potent agent in the treatment of human *trypanosomiasis* of the African type (p 531)

Absorption Distribution and Excretion—*Arsphenamine neoarsphenamine* and *silver arsphenamine* are given intravenously administered by other parenteral routes they are rapidly broken down into irritating oxidation products *Sulfarsphenamine* and *bismarsen* are more stable and may

For intrapleural intrathecal or intraperitoneal instillation soluble sodium or calcium preparations may be used in concentrations of 10 000 units to 1 cc For local and topical application depending upon the nature of the tissue ointments powders solutions troches lozenges dental cones or suppositories may be employed with gratifying results

Penicillin is excreted rapidly and in large amounts by the kidneys The maintenance of effective blood concentrations poses a problem that may be solved by continuous or frequent injection by the use of the slowly soluble



Fig 15B—Same case as that represented in figure 15A Complete recovery after treatment with penicillin

oil and wax mixture or by attempts to produce a renal blockade by simultaneous administration of diodrast or of 50 cc of 6 per cent sodium para amino hippurate The last raises plasma concentration from 0 02 to 0 2 units and increases the time factor from two to six hours

For the bed patient who is seriously ill the methods of choice are continuous intravenous drip or repeated intramuscular injections The ambulatory patient may return to the practitioner s office for repeated injections or he may be given a single daily injection of the mixture in oil and wax This

active effects are noted For this reason mapharsen which is essentially arsenoxide can be *given in smaller dosage as an effectual spirocheticidal* agent There is no waste, greater efficiency and lesser opportunity for toxicity

Toxicology—Untoward reactions to the arsphenamines may be early or late The various reactions depend on the mechanical effects of intravenous injections the colloidal nature of the drugs and the direct toxicity of the drugs

Early Reactions—The frequent early reactions are variously called *nitritoid anaphylactoid* and *angioneurotic* The symptoms and signs are chiefly of vasomotor origin During or shortly after the intravenous injection of an arsphenamine the face becomes flushed the conjunctivae are injected and the patient who appears anxious complains of palpitation dyspnea and a sense of substernal oppression Cough vomiting lumbar pain and chest pain are common the pulse becomes weak the blood pressure falls and unconsciousness may occur Some patients develop edema of the face larynx lips and tongue and widespread urticaria The symptoms disappear in ten to thirty minutes without treatment and are promptly relieved by subcutaneous injection of *epinephrine hydrochloride* (1 1000)

The cause of early reactions of the above type have been variously ascribed to adrenal damage and the colloidal nature of the drugs but they are clearly manifestations of *speed shock* and are avoided by slow injection particularly by the use of the intravenous drip

Other early reactions are due to the local effects of the intravenously administered drug With the exception of bismarsen and sulfarsphenamine the arsphenamines may cause local pain in the arm, thrombophlebitis and *extensive local necrosis if allowed to extravasate into the perivenous tissues*

Late Reactions—A wide variety of delayed systemic effects are observed during arsphenamine therapy These may affect the skin the liver the bone marrow and the central nervous system, singly or in combination

SKIN REACTIONS—A severe and at times fatal *dermatitis* may develop during arsphenamine therapy or several weeks after the last injection The eruption may be macular, maculopapular vesicular exfoliative or lichenoid and is almost always attended by malaise and fever *Pruritus* may precede the rash and is often present when the lesions are fullblown The mechanism *producing the various types of arsphenamine dermatitis has not* been established The major toxicodermas nearly always necessitate complete and permanent cessation of arsphenamine treatment *Exfoliative dermatitis* is particularly serious since the mortality rate is 25 per cent Sulfarsphenamine causes skin reactions with greatest frequency (Fig 16)

JAUNDICE—Jaundice is one of the commonest late reactions to arsphenamine therapy It may occur early in the course of treatment or after a long series of injections it may be a mild asymptomatic jaundice or a severe acute yellow atrophy The clinical picture usually is that of an acute toxic hepatitis but it may simulate an obstructive icterus The liver damage has been variously ascribed to a direct toxic action of the drug on the liver to syphilis to an intercurrent acute epidemic disease probably infectious or to various combinations of these factors

Jaundice is *most common* after arsphenamine and slightly less so after neoarsphenamine About 1 in every 125 patients receiving arsphenamine or

The Therapeutics of Penicillin and Streptomycin

(Compare with therapeutic activity of sulfonamide on pages 91 92 and 93)

Staphylococcus—With a few exceptions staphylococci are penicillin sensitive semi resistant strains may require large dosages for long periods of time Streptomycin less active

Streptococcus—Hemolytic varieties are penicillin sensitive *Str viridans* yields to penicillin in subacute bacterial endocarditis particularly when heparinization is simultaneously effected rheumatic fever is unaffected Streptomycin less active on hemolytic varieties but anaerobic types are sensitive (p 182)

Pneumococcus—With rare exceptions pneumococci are penicillin sensitive Intrapleural instillations are needed in empyema Streptomycin less active (p 206)

Meningococcus—With rare exceptions meningococci are penicillin sensitive The organism must be attacked by both systemic and intrathecal routes Streptomycin less active (p 216)

Gonococcus—With rare exceptions all strains of gonococcus even those which are sulfonamide fast are penicillin sensitive Streptomycin less active (p 229)

Enteric Bacilli—Typhoid paratyphoid dysentery colon bacilli and the vibrio of cholera are penicillin resistant but e coli is streptomycin sensitive to greater or lesser degree (p 225)

Mycobacteria—*M tuberculosis* and *M leprae* are penicillin resistant but streptomycin sensitive at least in the experimental animal (p 267)

Hemophilae—*H pertussis influenzae* and *ducreyi* are penicillin resistant *H influenzae* is streptomycin sensitive particularly in meningitis (p 94)

Anthrax—*B anthracis* is somewhat penicillin sensitive large doses over long periods of time are justified in conjunction with serum therapy Streptomycin is inactive (p 293)

Clostridia—*Cl tetani perfringens* and other participants in gas gangrene are strikingly sensitive to penicillin but antitoxin must be given to combat toxemia Streptomycin is inactive

C diphtheriae—*C diphtheriae* is penicillin sensitive The use of the remedy is justified in conjunction with antitoxin Streptomycin is inactive (p 311)

Botulism—*Cl botulinum* is penicillin sensitive but the use of antitoxin must not be overlooked Streptomycin is inactive

Brucellosis—*Br melitensis* is penicillin resistant Streptomycin exhibits some activity experimentally but clinical tests are disappointing (p 3 0)

Pasteurellae—The pasteurellae of plague (pestis) and tularemia (tularensis) are penicillin resistant Tularensis is particularly streptomycin sensitive (p 326)

Klebsiella (*B mucosus capsulatus*)—The Friedlander organism is relatively insensitive to penicillin but sensitive to streptomycin (p 328)

Miscellaneous Bacteria—The organism of erysipeloid is penicillin sensitive *B subtilis Proteus vulgaris Aerobacter aerogenes* and *Pseudomonas aeruginosa* are usually streptomycin sensitive

Spirochetes—*Tr pallidum* of syphilis is amazingly sensitive to penicillin the remaining treponemas borrelia leptospira and spirilla are also penicillin sensitive Streptomycin in larger doses seems less active as compared to penicillin (p 349)

Rickettsiae—The rickettsiae are but slightly penicillin-sensitive Streptomycin appears even less active (p 360)

Viruses—The viruses are penicillin resistant and streptomycin resistant (p 387)

Fungi—Actinomyces are penicillin sensitive other fungi appear to be resistant Streptomycin is inactive (p 489)

Protozoa—Plasmodia amebae leishmanias and trypanosomes appear to be penicillin resistant Streptomycin is inactive (p 506)

Helminths—The helminths are penicillin resistant Streptomycin is inactive (p 537)

In this respect sulfarsphenamine and neoarsphenamine are the principal offenders

Hemorrhagic encephalopathy is a rare late post arsphenamine reaction Headache vertigo mental excitation vomiting delirium incontinence

TABLE 15 —COMPARISON OF ORGANIC ARSENICALS

	Ars phen amine	Neoars phen amine	Silver ars phena amine	Sulfars phen amine	Bis marsen	Maphar en	Trypar samide
Trivalent	+	+	+	+	+	+	
Pentavalent							+
Contains bismuth					+		
Requires alkalinization	+						
Full therapeutic dose in mg	400	600	300	400	200	60[1]	3000
Bulk of therapeutic dose in cc	100	15–20	60	5–20	2	2[2]	10–20
Arsenic content per therapeutic dose (in mg)	120	120	60	76	26	18[3]	7 0
For intravenous use	+	+	+		[4]	+	+
For intramuscular use		+[5]		+[5]	+[5]		+[5]
Toxicity on standing	+	+	+				
Is colloid	+	+	+	+	+	[6]	+
Is crystalloid						+[6]	
Toxicity	High	Less	High	High	Low	Least	High
Spirochetal activity	Good	Good	Poor	Poor	Poor	Good[7]	Poor

NOTES ON TABLE 15

[1] The full single therapeutic dose of *mapharsen* is only $\frac{1}{6}$ to $\frac{1}{10}$ that of other preparations only mapharsen delivers arsenoxide in spirocheticidal potential others require changes in body hence arsenic wastage

[2] Only *mapharsen* of intravenous preparations can be given in ordinary 2 cc syringe *arsphenamine* by contrast requires intravenous infusion set

[3] The arsenic content of the full therapeutic dose of *mapharsen* is $\frac{1}{4}$ to $\frac{1}{10}$ of other arsenicals intended for intravenous use

[4] *Sulfarsphenamine* and *bismarsen* cannot be given intravenously with safety

[5] *Neoarsphenamine* *sulfarsphenamine* *bismarsen* and *tryparsamide* can be given intramuscularly

[6] Only *mapharsen* is crystalloid making for lesser toxicity

[7] Only arsphenamine neoarsphenamine and mapharsen are effectively spirocheticidal

convulsions and coma dominate the clinical picture and death may occur within one or two days after the onset The cause of this reaction is not known It is probably not a Herxheimer reaction since it has been observed in nonsyphilitics who have been given arsphenamine The delayed onset after injection eliminates the possibility of an anaphylactoid reaction

action must differ since an organism resistant to one may be sensitive to the other

The practitioner is constantly confronted with the problem of whether to use one or both of these modalities In general except in the ambulatory patient and those who require the insoluble sulfonamide for direct action on the lower bowel we favor the use of penicillin mainly because of its freedom from toxicity Unless the patient is seriously ill we advocate the use

Table 14—Comparative Efficacy of Penicillin and Sulfonamides

	Penicillin	Sulfonamide
Efficacy (wt for wt)	4-20 times stronger	
Effect of blood pus bacteria peptone and glucose on local use	None	Inhibition of action
Local toxicity	None	May be considerable
Delayed wound healing	No	Yes
Inhibition by para aminobenzoic acid	No	Yes
Available for oral use	Yes	Yes
Available for subcutaneous use	Yes	By hypodermoclysis
Availability for intramuscular us	Yes in 2-3 c doses	Only in great bulk
Available for intravenous use	Yes in 2 or cc syringe	Yes but requires 20 cc syringe or intravenous set
Insoluble preparations for bowel	No	Yes
Systemic toxicity	Negligible	May be considerable
Dermatoses	Rare	May be frequent
Blood dyscrasias	No	May occur
Drug fever	Rare	May be frequent
Patient may become sensitized	No	Yes
Organisms may become resistant	Occasionally and slowly	More often and quicker
Laboratory controls needed	No	Yes blood and urine examination
Patient may self medicate	Yes	Yes

of penicillin alone reserving sulfonamide for those who do not give a favorable response within thirty six to forty eight hours Naturally when the patient is desperately ill the practitioner combines the anti infective agents so that the full impact of the therapeutic program is felt at the earliest possible moment

Penicillin and Streptomycin—When the nature of the invading microorganism is not clear and the patient is desperately ill there is no harm in combining penicillin with streptomycin In this manner blanket coverage

pressure and a fall in circulating blood volume they may lead to shock Depression of the cardiac muscle contributes to the onset of circulatory difficulty The hyperemia of the intestinal tract caused by therapeutic doses of arsenic is probably the basis for its tonic use to increase the appetite and promote digestion Large doses produce acute gastro enteritis and ulcerations of the mucosa of the stomach and intestinal tract Vomiting frequently occurs and is usually bloody Arsenic is *nephrotoxic* producing injury to the glomerular capillaries and renal tubules The renal damage is reflected in the albuminuria cylindruria and hematuria of arsenic poisoning

The capillary dilatation caused by arsenic is believed to enhance the *nutrition of the skin For this reason arsenic is administered to improve* the complexion The coats of domestic animals are improved and become thick and glossy Small doses of arsenic are said to stimulate the central nervous system in an obscure manner Larger chronic doses cause peripheral neuritis and spinal cord injury large single doses produce a fatal depression of *the respiratory center in the medulla*

Small doses of arsenic increase the vascularity of the bone marrow and lead to an increase in the number of immature cells in the peripheral blood particularly in certain types of anemia large doses inhibit hematopoesis When the formation of leukocytes is excessive as in leukemia, arsenic inhibits the formation of these cells

Poisoning—The signs symptoms and treatment of *acute* and *chronic arsenic* poisoning are dealt with in the section on toxicology (p 752)

Therapeutics—Inorganic arsenic is used chiefly in the treatment of *psoriasis* (p 3414) and *leukemia* (p 1100)

Bismuth—Bismuth has a spirocheticidal and spirochetostatic effect and is a demonstrably able adjuvant to arsenic in the treatment of *syphilis* (p 344) The insoluble salts of bismuth are excellent local protectives and are discussed with the Digestive System (p 1756)

Absorption Distribution and Excretion—Bismuth preparations effective in syphilis are given by intramuscular injection Absorption from the gastro intestinal tract and from the skin (inunction) is not satisfactory The compounds with the best spirocheticidal value are capable of maintaining the continued excretion of 0 002 gm of metallic bismuth daily in the urine

After injection bismuth is distributed to all tissues of the body Large amounts are found in the kidney and liver That it passes the placental barrier and enters the fetal tissues is indicated by the occurrence of bismuth lines in the long bones of infants whose luetic mothers received the metal during gestation

Excretion occurs largely by way of the urine but a small amount (10 per cent) appears in the feces The urine concentration depends on the blood *concentration The latter reflects the rapidity of absorption* from muscular depots into the circulation The excretion of water soluble and water miscible preparations occurs to a large extent within twenty four hours On the other hand oil suspensions of insoluble bismuth compounds (subsalicylate) are excreted slowly over the course of weeks A satisfactory preparation for use in syphilis allows a continuous daily excretion of 2 to 4 mg of bismuth in the urine during the course of bismuth therapy (Cole)

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TABLE 16 —BISMUTH PREPARATIONS FOR ANTILUETIC THERAPY

Form	Preparation	Nature	Dose
Water solution	Bismosol	Potassium sodium bismuthotartrate in a 10% aqueous glucose solution Contains 35% bismuth	1 cc every 2 days until 20 doses are given Repeat course after a rest period of a month
	Bismuth sodium tartrate	1.5–3 0% of the drug in a 25% sucrose solution with benzyl alcohol	0 03 gm 2 or 3 times weekly for 6–10 weeks
	Potassium bismuth tartrate	2.5% aqueous solution containing cresol 0 2% and sucrose 6%	50 mg every 2–3 days until 12–18 injections have been given
	Thiobismol	Sodium bismuth thioglycollate 0 2 gm in 1 cc of distilled water Contains 38% bismuth	0 2 gm 3 times weekly for 12–15 doses (adult)
Solution in organic solvent	Iodobismitol with saligenin	Sodium bismuth iodide (6%) in propylene glycol with sodium iodide (10%) saligenin (4%) and 0 1% acetic acid (glacial)	2 cc every 3 days in courses of 14–16 injections
	Sobisminol solution or mass	Product of interaction of sodium bismuthate tri isopropanolamine and propylene glycol in a mixture of propylene glycol and water Contains 20 mg bismuth per cc	2 cc biweekly in courses of 20–25 injections Also available as sobisminol mass for oral use capsules representing 150 mg are taken in daily dose of 6 to 9 for 10 to 12 weeks
Oily solution	Bismocymol	A basic salt of camphocarboxylic acid containing 37–40% bismuth in olive oil Each cc contains bismocymol equivalent to 50–100 mg metallic bismuth	Doses representing 100 mg of metallic bismuth once a week or 50 mg biweekly for 6–8 weeks
Suspension in oil	Bismuth subsalicylate	10% bismuth subsalicylate suspended in vegetable oil to which a local anesthetic is added	0 2 gm weekly
	Oleo Bi	A suspension of finely divided bismuth oleate in olive oil containing bismuth oleate equivalent to 50 mg of bismuth per cc	2 cc once a week in courses of 12–20 injections
	Potassium bismuth tartrate	10% suspension of bismuth potassium bismuthotartrate in peanut oil with 0 4% butyn Contains equivalent of 66 mg of metallic bismuth per cc	0 1 to 0 2 gm weekly until 2 4 to 3 0 gm have been given

metal tend to accumulate in the kidney renal damage is common when the urinary excretion approaches high levels (over 10 mg daily)

The alimentary excretion is irregular The metal enters the small

3 In every genus of bacteria there are sensitive and resistant strains sulfonamides cure gonorrhea in 60 to 80 per cent of instances but 20 to 40 per cent of patients are not cured since the infecting organism is sulfona mide fast If the general biological principle of resistant strains in a sus ceptible genus is acceptable may there not be the possibility that there is an occasional sensitive strain in a reputedly resistant genus? May the prac titioner not witness occasionally a specific therapeutic result with an iso lated patient despite contrary laboratory and statistical evidence?

4 Since penicillin and streptomycin have no appreciable toxicity the administration of these remedies to a patient who is desperately ill may accomplish good with little risk of the production of evil The same cannot be said of the sulfonamides in which instance the hazard of toxicology must be weighed in the balance

5 The practitioner who deals with individuals not with cases or statis tics may be guided by the thought that it is better that a thousand corpses be wastefully saturated with penicillin and streptomycin than that there should be one lacking these drugs whose life might have been saved by their unorthodox administration

Other Antibiotics

Actinomycin A—Actinomycin A is a red pigment soluble in ether ethyl alcohol and water It contains 13 per cent nitrogen but is not a protein and has no free amino groups It has been crystallized

Actinomycin A has a powerful bacteriostatic and bactericidal action in vitro on many gram positive bacteria It is less effective against gram negative organisms Actinomycin A is unfortunately extremely toxic for laboratory animals it appears to lack in vivo activity against hemolytic streptococci pneumococci and *Brucella abortus* From its toxicity in ani mals and lack of activity in vivo it would not appear to offer great prom ise in the systemic treatment of bacterial infections

Actinomycin B—Actinomycin B is a second fraction isolated from *Actinomyces antibioticus* It is weakly bacteriostatic but in high concentra tions is bactericidal against some organisms

Bacitracin—Bacitracin derived from B subtilis promises to be as effec tive as penicillin in the treatment of local infections caused by staphylo cocci streptococci and the gas gangrene group The substance seems to be thermostable water soluble and relatively nontoxic when applied locally or subcutaneously

Citrinin—Citrinin is a derivative of another penicillium like aspergillin its toxicity precludes clinical consideration

Clavacin—Clavacin possesses antibiotic activity against many patho gens it was enthusiastically proclaimed under the name of Patulin for local use in the treatment of the common cold More sober trials appear less conclusive and toxicity is a real hazard

Flavicin—Flavicin is a derivative of a mold contaminant obtained from a culture of penicillin It exhibits activity against staphylococci *C diph theriae B anthracis* and *B abortus* but its extracts are toxic to mice

Streptothricin—Streptothricin is obtained from soil actinomyces It is soluble in water insoluble in ether destroyed by concentrated acids but not by proteolytic enzymes It withstands boiling and its properties appear to be those of an organic base It is highly bacteriostatic and bactericidal in vitro against a number of gram negative organisms

TABLE 16.—BISMUTH PREPARATIONS FOR ANTILUETIC THERAPY

Form	Preparation	Nature	Dose
Water solution	Bismosol	Potassium sodium bismuthotartrate in a 10% aqueous glucose solution Contains 3.5% bismuth	1 cc every 2 days until 20 doses are given Repeat course after a rest period of a month
	Bismuth sodium tartrate	1.5–3 0% of the drug in a 25% sucrose solution with benzyl alcohol	0 03 gm 2 or 3 times weekly for 6–10 weeks
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leads to salivation and frequently to a mild stomatitis This may be the result of a stimulation of the salivary glands or the response to the irritation of the oral mucosa by the mercury present in saliva The stomatitis usually takes the form of shallow ulcerations These are easily infected Necrosis of the jaw may eventually result

Administration—Suspensions of mercury in fat are rapidly absorbed when *rubbed into the skin* The mercury penetrates deep into the sweat glands and hair follicles and gains ready access to the circulation Sufficient metal can be introduced by this method to saturate the body within two weeks The advantages of this method are that it is painless and intestinal disturbances are avoided The method is very safe and the amount of metal absorbed daily is fairly constant The obvious disadvantages are that it is dirty time consuming and frequently productive of skin irritation

Solutions of soluble mercuric salt or pills containing an insoluble mercurous salt or metallic mercury may be given *orally* The soluble salts are rapidly and completely absorbed The absorption from insoluble compounds is less but still appreciable The oral route is attended by a high incidence of gastric disturbance and the invariable occurrence of diarrhea

Deep injection into the gluteal muscles is a popular mode of giving mercury especially in treating syphilis Intramuscular injection is painful but the body can be saturated rapidly and effective concentrations can be maintained for long periods Since cumulative effects are easily produced periods of treatment must be separated by rest periods These rest periods allow for the gradual release and excretion of mercury from the sites of intramuscular injection

Mercury Poisoning—The signs symptoms and treatment of acute and chronic mercury poisoning are dealt with in the section on *Poisoning* (p 765)

Preparations—Soluble inorganic and simple organic mercury salts are used as disinfectants and antiseptics and have a limited use in the treatment of syphilis

MERCURIC CHLORIDE (CORROSIVE SUBLIMATE)—This is a heavy white powder which is readily soluble in water (1 13 5) It is incompatible with almost all other substances It is used almost exclusively to disinfect inanimate objects (1 1000 solution) and to cleanse the unbroken skin (surgeon s handwash preliminary disinfectant of skin of external genitalia prior to catheterization (1 2000 solution) A 1 500 solution in 50 per cent alcohol is an effective agent against *pediculosis capitis* Small doses in pill form (4 mg or 1/16 grain) are used as an antisyphilitic remedy Mercury bichloride is supplied in the form of large (0 5 gm or 7¼ grains) and small (0.25 gm or 4 grains) poison tablets (U.S.P) These are dyed blue and are coffin-shaped to aid in the recognition of the poison It is a good clinical rule to remember that "*a blue stained vomitus in an acutely ill patient suggests mercuric chloride poisoning*

MERCURIC CHLORIDE SUBSTITUTES—A considerable number of soluble organic salts of mercury have been introduced in an attempt to provide compounds that are less toxic Many of these have been included in N.N.R., but it is doubtful whether they provide any tangible advantages over the older preparation

1 MERCURY BENZOATE—This salt is said to be less corrosive than mercuric chloride and has the same general uses A 1 2000 solution is used to irrigate the urethra in *gonorrhea* A 1 per cent solution is given intramuscularly in syphilis

2 MERCURIC CYANIDE—This compound is the salt of hydrocyanic acid It is used locally (1 4000 solution) for application to the *eye* and other *mucous membranes* It has been given internally as a diuretic but is inferior to the organic mercurials

perivenous extravasation Should this occur immediate aspiration of the area and injection of physiological saline is recommended to prevent tissue damage

Arsphenamine is given in doses of 0 3 to 0 4 gm (4½ to 6 gr) to adult males in the treatment of syphilis The number and frequency of individual doses varies with the clinical course of syphilis (p 342)

Neoarsphenamine U S P has essentially the same structure as arsphenamine except for the addition of a methylene sulfoxylate group to an amine It is dispensed as the sodium salt according to the following formula

NEOARSPHENAMINE—Consists chiefly of sodium 3 3-diamino 4 4-dihydroxyarsenobenzene-N methanal sulfoxylate It contains not less than 19 per cent of arsenic (As) and complies with the requirements of the National Institute of Health U S Public Health Service U S P



Neoarsphenamine U S P is a derivative of arsphenamine It is a yellow powder which dissolves in water to give a solution which is neutral to litmus It is supplied in vacuum ampoules which should be kept in an ice box Neoarsphenamine is very unstable and readily deteriorates into toxic products when exposed to air

Neoarsphenamine may be given by intravenous or intramuscular injection The former route is preferable In using the drug the following procedure (N N R) should be followed

The ampoule containing the drug is immersed in alcohol to detect a possible crack then carefully wiped off the neck is filed across and broken off and the contents sprinkled on the surface of cool sterile distilled water and allowed to dissolve without shaking the solution Any product incompletely soluble should be discarded Solutions of neoarsphenamine must be injected immediately after their preparation The temperature of the injected fluid should not be more than 20 to 22 C The amount of water used is from 2 to 10 cc per 0 1 gm of drug A total of 15–20 cc is usually employed Agitation to effect solution increases toxicity Injection is made slowly at a rate of not more than 0 1 gm per 30 seconds For intramuscular and subfascial injections 3 cc of freshly distilled water should be used for each 0 15 gm of neoarsphenamine thus yielding an approximately isotonic solution

Since neoarsphenamine is less toxic than arsphenamine and contains less arsenic larger doses are used The average dose is from 0 45 to 0 6 gm (7–9 gr) for the average male A slightly smaller amount is given to women Children are given 0 1 to 0 2 gm (1½ to 3 gr)

Silver arsphenamine (N N R) is an amorphous brownish black powder which readily forms a clear deep brown solution slightly alkaline to litmus It contains 19 per cent arsenic and from 12 to 14 per cent of silver It is marketed as the sodium salt in the sealed ampoules The drug is always given intravenously In preparing the solution for injection the ampoule is first tested for cracks by immersion in alcohol for 15 minutes, after open

dead or dying In this case it will penetrate A 1 per cent aqueous solution is used to irrigate the bladder

2 MERTHIOLATE—This is a complex thiosalicylate containing 49 per cent mercury in organic combination It is germicidal against nonsporing bacteria and is useful in disinfecting tissue surfaces A 1 1000 aqueous solution is used to disinfect instruments and for application to wounds and denuded surfaces A 1 5000 to 1 10 000 solution is used in the eye Solutions of 1 5000 to 1 20 000 are used in the genitourinary tract It may be applied to the cervix and vaginal mucosa

3 METAPHEN—This is a complex organic compound containing 50 per cent mercury in organic combination It is relatively nonirritating and does not corrode rubber or surgical instruments Its toxicity is low Solutions of 1 1000 to 1 5000 are used for disinfecting instruments and for application to the skin Solutions of 1 5000 to 1 10 000 are proposed for irrigating the eye or the urethra Sodium hydroxide must be added to metaphen to dissolve it

4 MERCURIAL DIURETICS—These complex organic mercurials are among the best available diuretics They are described in the section on diuretics (p 261)

Antimony—Although antimony had been known to the medical profession and to the laity as a powerful poison it was not until the beginning of the present century that the chemotherapeutic value of this metalloid was recognized Within the last thirty years a series of antimony compounds have proved effective agents in the treatment of a score of parasitic diseases including some of the commonest infestations of modern man particularly *leishmaniasis schistosomiasis filariasis trypanosomiasis* and *lymphogranuloma venereum* Due to relative infrequency of these conditions in this country, the average physician has little opportunity for practical experience with the antimony compounds

The antimony drugs in modern use are all synthetic organic compounds which like the organic arsenicals may be divided into the trivalent and pentavalent groups Inorganic antimony is never employed because of its extreme toxicity The trivalent organic compounds are quite toxic but at the same time are more valuable as parasiticides The toxicity and parasiticidal activity are related to the liberation of inorganic trivalent antimony The trivalent substances may be used whenever there is an indication for antimony therapy The pentavalent drugs are of value in leishmaniasis and schistosomiasis Their chief advantage is the lower toxicity which enables larger amounts of antimony to be given in a single dose These compounds sometimes cure infections resistant to therapy with trivalent antimony

General Pharmacology—Compounds that liberate antimony are very irritating to the skin and mucous membranes They may cause papular vesicular and pustular eruptions This irritant action is the basis for the ability of antimony salts particularly the tartrates to cause emesis when in contact with the mucosa of the stomach Toxic doses cause emesis by an action on the central nervous system

Subemetic doses of antimony cause a reflex stimulation of the salivary and bronchial glands and give rise to nausea and expectoration This expectorant action accounts for the inclusion of antimony in many expectorant mixtures

MODE OF ACTION AGAINST PROTOZOA—The antimony derivatives are not parasiticidal in vitro Although the exact mechanism is not known the metalloid acts to allow the natural defense mechanisms to eradicate the parasitic invaders

Mapharsen is a partial oxidation product of arsphenamine with the following formula





The compound possesses certain unique physicochemical properties: it is a pure *crystalline* substance which is readily soluble in neutral, acid or alkaline solutions. Its crystalline nature and chemical stability greatly simplify its clinical use.

Mapharsen (meta-amino-para-hydroxyphenylarsine oxide) is an oxidation product of arsphenamine. Ehrlich, who originally studied this compound, believed it to be the oxidation product through which the various arsphenamines exerted their parasiticidal action in the body. Although it was once believed to be too toxic for clinical use, recent clinical studies indicate that it is the best of the antiluetic compounds (Table 15, p. 174).

Mapharsen is a white amorphous, odorless powder containing 29 per cent trivalent arsenic. Solutions are neutral and crystalloid rather than colloid, thus they are free from the reactions due to the colloidal physical properties of other arsphenamines. Mapharsen is equal to arsphenamine in therapeutic potency at dosage levels of arsenic which are much lower. It is soluble in water, alcohol, acids, alkalies and alkali carbonates; the aqueous solution is acid to methyl red but alkaline to congo red. Mapharsen is marketed as the hydrochloride in nitrogen-filled ampoules. These contain sufficient anhydrous sodium carbonate to neutralize the acid salt and sufficient anhydrous purified sucrose to make the solution isotonic with the blood. The sealed ampoules keep indefinitely.

After a careful inspection the ampoule is opened aseptically and 2 cc. of sterile distilled water are introduced. Solution is prompt and slight effervescence occurs. The solution is drawn into a sterile syringe and is ready for injection. Aeration, exposure to air and boiling for one minute do not increase toxicity but a brown color appears on prolonged standing.

Mapharsen is given intravenously fairly rapidly (1 – 6 seconds) when the smaller quantities are used by the syringe method. Mapharsen is the drug of choice in the continuous intravenous drip massive dose therapy of early syphilis ("Five Day Treatment").

The average adult dose of mapharsen is 60 mg. (1 gr.) which is about one-tenth the dose of arsphenamine. The drug is excreted rapidly in the urine and injections may be repeated every four or five days since the danger of cumulative toxicity is slight. In children the initial dose should not exceed 0.5 mg. per Kg. of body weight; subsequent doses may be increased to 1 mg. per Kg.

Clorarsen is the most recently accepted trivalent arsenical (dichlorophenarsine hydrochloride). It is marketed in ampoules containing 0.045 and 0.067 gm. (N.N.R.). On addition of distilled water a reaction takes place with the formation of arsenoxide comparable to mapharsen. The initial recommended dose is 0.03 gm. for women and 0.04 gm. for men given intravenously. Subsequent doses may be increased to 0.04 gm. for women and 0.068 gm. for men.

Antimony Poisoning—Acute and chronic antimony poisoning are rare. For a description of the findings see section on Poisoning (p 752)

Silver—Silver compounds possess important local actions The liberation of free silver ions precipitates protein and produces caustic astringent and antiseptic effects Silver compounds may be divided into two general groups (1) *Simple soluble silver salts* which readily dissociate and (2) *colloidal preparations* in which the amount of free silver ions is very small The action of the first group is caustic and corrosive since the concentration of ionic silver is high The action of the latter group is one of mild continuous antiseptic action and is only mildly bactericidal Metallic silver exerts a marked bactericidal effect when present in aqueous solution in a minute amount (1 20 million) This is known as *oligodynamic action* and occurs with other heavy metals

Soluble Silver Salts SILVER NITRATE—Silver nitrate is the most commonly used silver salt It is an effective *caustic germicide antiseptic* and *astringent* When added to solutions of proteins it forms a heavy silver proteinate which is an effective antiseptic since silver ions are given off The presence of sodium chloride interferes with the action of the silver ions by precipitating the insoluble silver chloride The presence of chloride ion in the tissue fluids limits the effectiveness of the ionized silver

In solid form silver nitrate is used to cauterize wounds warts and granulation tissue It is supplied in convenient sticks Solutions of various strengths are employed for local antiseptic action A 10 per cent silver nitrate solution is used with tannic acid in the treatment of *burns* A few drops of 1 per cent silver nitrate instilled in the conjunctival sac are given at birth to prevent *ophthalmia neonatorum*

SILVER LACTATE—Silver lactate is used for the same purposes as silver nitrate in dilution of 1 100 to 1 2000

SILVER PICRATE—Silver picrate is a yellow insoluble powder which is used chiefly in the treatment of *trichomonas vaginitis* It is usually applied in powder form by means of a powder blower (1 part silver picrate plus 99 parts of purified kaolin) The salt is also supplied in a boroglyceride gelatin base in the form of suppositories

Colloidal Silver Preparations—Although colloidal silver compounds are noncorrosive relatively non astringent and non irritant, they liberate sufficient silver ions to exert an antiseptic action The preparations are produced by dissolving reduced silver or silver oxide or some protein silver precipitate in an excess of a denatured protein and drying in vacuo This results in substances that dissolve slowly but freely to form ' colloidal solutions which contain so little free silver ion that they do not readily precipitate chloride or protein The following therapeutic groups are recognized Protein Silver Strong Type Protein Silver Mild Type Collargol Type Electric Type Silver Halides

The *strong type* of silver protein contains 7.5 to 8 per cent silver but has strong germicidal and irritant actions *Protargol* is an example of this group The solutions should be freshly prepared and dispensed in amber colored bottles

Mild silver protein compounds contain 19–25 per cent silver but are relatively nonirritant As in the case of the strong type they should be prepared fresh and should be dispensed in amber colored

be absorbed from an intramu cular site All arsphenamines are poorly ab sorbed from the gastro intestinal tract

After intravenous injection the arsphenamines are rapidly removed from the circulating blood Apparently the liver is the chief storehouse but large amounts are found also in the spleen The liver seems to be in volved in the conversion of the arsphenamines to more active oxidation products (arsenoxide) and slowly releases the active spirocheticidal frac tion to the blood stream Most of the arsenical is excreted within a week A small fraction remains in the body especially in the skin and the skele ton and is capable of causing chronic arsenic poisoning

The various arsphenamines penetrate the central nervous system and appear in the spinal fluid to varying degree Arsphenamine is found in higher concentration in the spinal fluid than in the blood silver arsphena mine tends to enter the spinal fluid with greatest facility while neoarsphena mine is intermediate There is no correlation between arsenic concentrations in the spinal fluid and the efficacy of the various drugs in the treatment of central nervous system syphilis Tryparsamide which causes the least accumulation of arsenic in the spinal fluid is the best of the arsenicals in the therapy of neurosyphilis

After arsphenamine injections arsenic is largely excreted in urine and feces only small amounts appear in the saliva sweat and milk Urinary excretion starts within a few hours after injection but the greater part of arsphenamine is excreted by way of the bile into the stool

Mode of Action—The arsphenamines are not directly parasiticidal since very high concentrations of the various drugs do not reduce the growth or motility of the organisms in vitro The chemotherapeutic action depends upon the participation of the tissues of the host which change the arsphenamine molecule to *arsenoxide* an oxidation product similar to mapharsen This latter compound is *trypanocidal* in vitro The conversion of arsphenamine to arsenoxide is responsible for the latent period of several hours before the parasites are cleared from the blood The exposure of solu tions of arsphenamine allowing oxidation renders them extremely toxic Only a small percentage of arsphenamine is transformed into arsenoxide and a larger amount is changed to other compounds resulting in consider able waste in contradistinction to mapharsen

Arsenoxide apparently acts by interfering with the cellular respirations of the parasite According to Voegtlin the action of arsenic is essentially due to an interference with the normal function of glutathione in the oxidation reduction phenomena of the tissues Parasites are more suscepti ble to this action but the cells of the host are also injured to some extent and may even be killed This may explain the occurrence of the wide variety of toxic reactions Certain undesirable side actions may be due to the presence of unrecognized by products of arsphenamine

Therapeutics—The organic arsenicals are employed in the *treponema toses* notably *syphilis* and in *trypanosomiasis* and *amebiasis* The individ ual indications are taken up in the discussions of the treatment of each of these conditions In general it may be noted however that only arsphena mine neoarsphenamine and mapharsen are actively trypanocidal In the instance of arsphenamine and neoarsphenamine it is necessary for the body tissues to alter the arsphenamine to the form of arsenoxide before

USES OF COLLOIDAL SILVER PREPARATIONS —Colloidal silver preparations are used to produce *mucous membrane antisepsis* Strong silver protein acts principally as a demulcent and protective Strong silver protein (? per cent) is a valuable prophylactic for venereal disease when used with soap and water and 30 per cent calomel ointment The various uses of these compounds are listed in Table 17

Argyria —The careless use of silver preparations leads to the accumulation of silver in the body and the production of a condition known as *argyria* The absorbed silver accumulates in the subcutaneous connective tissues and on exposure to light produces bluish black pigmentation Perhaps the most common cause of argyria is the use of colloidal silver preparations Silver arsphenamine accounts for an occasional case and industrial exposure for a few more

The clinical picture is characterized by the appearance of a blue line on the gingival margins This is difficult to distinguish from a lead or bismuth line The exposed skin becomes gray and may turn a deep vivid blue The pigmentation is irreversible but produces no systemic injury The sclerae may be tinged a bluish gray or a brownish black Treatment which is rarely successful involves the local intradermal injection of 6 per cent sodium thiosulfate solution and a 1 per cent solution of potassium ferrocyanide

Para aminobenzoic Acid —Recognition of the antibiotic value of para aminobenzoic acid furnishes another of the startling paradoxes of chemotherapy Used first as an inhibitor of sulfonamide activity in bacterial cultures it has proven of clinical efficacy with inapparent toxicity in the treatment of intra cellular invasions particularly by rickettsia

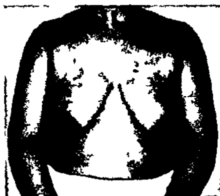
In typhus Rocky Mountain Spotted Fever and Tsutsugamushi Fever (p 369–386) an initial oral dose of 4 0 to 8 0 gm (60 to 120 grains) followed by 2 0 gm (30 grains) at two-hour intervals has produced extraordinary results The drug may cause nausea and vomiting unless given with ample fluid and bicarbonate of soda These doses effect and maintain blood concentrations of 10 to 20 mg per 100 cc and are continued until the rectal temperature remains below 99 5° F for at least one day

Para aminobenzoic acid may be prescribed with penicillin and streptomycin but must not be given with sulfonamides

neoarsphenamine develops jaundice Tryparsamide mapharsen and silver arsphenamine cause jaundice with less frequency

The occurrence of jaundice necessitates the cessation of arsenical therapy After a rest period of several months therapy may be resumed cautiously using small doses The treatment is that of toxic hepatitis

BONE MARROW DEPRESSION —The organic arsenicals may depress the function of the bone marrow Any or all of the hematopoietic structures may be affected causing *thrombocytopenia granulocytopenia* or *aplastic anemia* The marrow injury results from the combined toxicity of arsenic



A



B

Fig 16 —Arsenical dermatitis

and compounds possessing the benzene ring Thrombocytopenia is seen more commonly after neoarsphenamine which is apparently capable of injuring platelets in the peripheral blood The incidence of the other types of reaction is highest with sulfarsphenamine Tryparsamide has not been a cause of reactions of this type

Aplastic anemia is especially serious and is attended by a mortality of 80 per cent The only known treatment is supportive and consists of repeated blood transfusions

NERVOUS SYSTEM REACTIONS —The organic arsenicals may cause a mild *polyneuritis* which usually disappears after the drug has been discontinued

subsequently Capsules vary considerably in their chemical composition Most bacterial capsules that have been studied chemically consist of *poly saccharides* some of which contain nitrogen while others are entirely nitrogen free The capsule of hemolytic streptococci (Group A) contains hyaluronic acid

The *cytoplasm* of the bacterial cells is undoubtedly differentiated although in most organisms it appears homogeneous What appear to be *nuclei* have been demonstrated by the electron microscope *Granules* and *polar bodies* are brought out by differential stains *Spores* occur in certain species (anthrax tetanus) when circumstances are unfavorable to bacterial growth and activity



Fig 17—Electron microscope photograph of *Hemophilus pertussis* (× 50 000) Actually the bacterium that causes whooping cough is about 0.5 micron in length this is approximately equivalent to 0 0000195 inch The bacterial body shown is enveloped by a membrane or capsule which shows as a lighter surrounding area The capsule of *H pertussis* is antigenic *

Bacteria are identified most easily through the use of *stains* Those in most common use include the simple coloring with *methylene blue* the differential *Gram* and the *carbolfuchsin acid fast stains* (p 52)

Reproduction of Bacteria—Reproduction of bacteria is accomplished by *binary fission* The organism gradually increases in size and becomes constricted in the middle The constriction deepens until finally the content are held in two separate compartments The two new cells remain adherent for a time but sooner or later they separate and form new daughter cells

* Dr Malcolm H Soule in Therapeutic Notes May-June 1943 Parke Davis & Company

A chief danger from tryparsamide is *optic atrophy* which occurs with even greater frequency when atoxyl is used In some cases tryparsamide causes sudden blindness but in most instances visual symptoms and contraction of the visual fields warn of the imminence of optic nerve injury

The Choice of Organic Arsenical—We favor the use of mapharsen in any indication for which there is need for the injection of an organic arsenical The accompanying table summarizes the principal data on which this dogmatic opinion is based In brief mapharsen is chosen for convenience since it can be given by intravenous injection using an ordinary 2 cc syringe it has the advantage of being crystalline and stable in solution form the therapeutic dose is relatively small and of considerably less arsenic content than the other effectively spirocheticides its toxicity is relatively slight and its spirocheticidal activity is relatively great In the conduct of our work on the intensive arsenotherapy of infectious syphilis (Five-Day Treatment) we were led to the inevitable conclusion that there was no comparable preparation

Arsenic Antidote—An anti arsenic chemical has been developed for use after poisoning with lewisite The substance called BAL is 2 3 dithiopropanol is injected intramuscularly in doses of 2.5 to 4 0 mg per kg (p 767) forming an arsenic compound innocuously excreted by the body

Inorganic Arsenicals—Inorganic arsenic is usually used in the form of *arsenic trioxide* (arsenous acid) which is a white powder moderately soluble in water (1 65) The compounds commonly prescribed are the *Solution of Potassium Arsenite* (Fowler s Solution) and the *Solution of Arsenous Acid* each contains 1 gm of arsenic trioxide in 100 cc of solvent

Absorption Distribution Excretion—Soluble salts of arsenic are readily absorbed from all mucous membranes and parenteral sites There is an appreciable absorption from percutaneous inunction The metal is deposited rapidly in the tissues and is stored chiefly in the liver kidney gastro intestinal tract spleen and lungs Small amounts enter the muscles and nervous system Prolonged administration leads to deposition in the hair and skeleton Arsenic is slowly excreted in the urine and in the feces and cumulative poisoning is very easy to produce

Pharmacology—Inorganic arsenic is a powerful general protoplasmic poison Its action is slow and there is usually a considerable latent period between administration and the appearance of toxic effects It is very likely that arsenic interferes with cellular respirations by poisoning an important oxidation reduction system The result is an arrest of cell division and death

LOCAL ACTION—Local application of inorganic arsenic to the skin and mucous membranes produces only mild irritation If left in contact with the skin for a long time considerable hyperemia vesication and necrosis occur Superficial neoplastic (cancerous) tissue is especially susceptible Arsenic workers show characteristic skin changes including proliferation (hyperkeratosis) atrophy degeneration and pigmentation

SYSTEMIC ACTION—Arsenic is very toxic to capillary endothelium causing widespread capillary dilatation increased permeability and thrombosis The vascular bed of the splanchnic area is particularly vulnerable The changes in capillary tone caliber and permeability result in lowered blood

Growth and Culturing of Bacteria—Special methods are desirable to favor the growth of bacteria for diagnostic reasons and for the preparation of vaccines and toxins The culture media must contain *foods* necessary for bacterial growth These are commonly supplied by using the soluble constituents of meat in the familiar meat infusion broth The reaction of media (*p*H) is adjusted to secure optimal bacterial growth The prepared media are *sterilized* before the bacteria are implanted

The usual culture media are liquid or solid the latter being prepared by the addition of 1 to 2 per cent *agar* to the broth base Those in common use include meat extract, enriched preparations containing gelatin casein milk, *potato serum tomato juice ascitic fluid, whole blood* various sugars (particularly dextrose) hydrocele fluid, egg sterile tissue (such as kidney or testis) and synthetic media made from amino acid mixtures and salts Completely synthetic media of known chemical composition are coming into wider use and may be purchased from reliable manufacturers

Various bacteria differ in their cultural requirements Some grow on simple media such as peptone water whereas others require enriched media The selection of the proper culture medium is a matter which requires the judgment of an experienced bacteriologist Most bacteria grow best in a slightly alkaline medium Some species are hardy and will survive over a wide range of hydrogen ion concentration while others are exacting and demand that the *p*H of the medium be rigidly controlled

Carbon Dioxide and Oxygen Requirements—The presence of an *increased* CO_2 *tension* in the environment favors the development of most bacteria especially in the early stages of growth For some organisms such as *Brucella abortus influenza bacillus meningococcus and gonococcus* increased CO_2 tensions are essential on the other hand many others initiate growth successfully in the presence of the small amount of CO that is present in atmospheric air

There are numerous devices for increasing the concentration of CO but the simplest is the *candle jar* In this procedure the inoculated plates or culture tubes are placed in a jar which contains a candle The candle is lighted and an air tight cover applied When the oxygen is exhausted the flame goes out At that time the concentration of CO_2 in the jar is usually about 3 per cent

Bacteria differ in their need for *oxygen Obligatory* aerobes grow only in the presence of free oxygen obligatory anaerobes obtain oxygen by enzymatic processes and are injured by the presence of free oxygen *facultative* aerobes and anaerobes grow in the presence or absence of oxygen The great majority of common pathogenic bacteria are in the last category Clostridia (tetanus and Welch bacilli) are obligatory anaerobes whereas *the hemophileae (influenza bacillus) and pasteurelleae* (plague) are obligatory aerobes

Anaerobic cultural conditions may be produced by sealing the culture tube with a layer of petrolatum by the mechanical removal of air and its replacement by hydrogen or nitrogen or by the chemical combustion of oxygen Efficient anaerobic jars have been devised (Fildes jar) which combine mechanical removal of air with chemical removal of molecular oxygen

Therapeutics—Bismuth is used in antiluetic therapy in the following forms (a) aqueous solutions (b) solutions in organic solvents (c) oily solutions (d) suspensions in oil and (e) suspensions in water Those included in N N.R are shown in Table 16 p 128

Toxicity—Bismuth rarely produces significant toxic reactions Intramuscular injections may be very painful and the amount of discomfort is minimized by the addition of local anesthetic to many of the available products Some bismuth compounds such as bismocymol may produce sufficient local irritation to cause a sterile abscess at the injection site

The injection of bismuth solution into a vein may result in shock and even a fatal termination Precautions should also be taken to see if blood can be aspirated before the intramuscular implantation is made

Bismuth may produce an obstinate *stomatitis* especially when large doses are used in the presence of poor mouth hygiene A bluish pigmentation develops at the gum margins and in the buccal mucosa and it persists for years after treatment has been stopped *Hepatomegaly* and *toxic hepatitis* have been reported Mild kidney damage may also be encountered as well as an occasional *toxicoderma* On occasions patients may complain after the injection of vague constitutional symptoms with malaise headache and arthralgia

Mercury—Mercury has been used in medicine since antiquity For more than four hundred years prior to the discovery of the organic arsenicals (1900) it was the sole agent available for the treatment of syphilis In recent years however the therapeutic importance of the metal has decreased steadily

General Pharmacology—The pharmacologic activity of mercury compounds depends largely on the amount and rapidity of the liberation of mercuric (Hg^{++}) ions The quantity of ionic mercury liberated in turn varies with the chemical nature of the individual compounds

The mercuric ion is a powerful general protoplasmic poison It is a strong protein precipitant and in addition has a direct toxic action on all living cells Consequently it is an intense irritant and corrosive The various tissues with which it comes in contact react with characteristic effects

Absorption Distribution and Excretion—Mercury enters the body via all the usual portals Soluble salts are absorbed from the gastro intestinal tract in oily vehicles the metal passes through the intact skin (inunction) mercury vapor is inhaled in toxic amounts by workers in certain industries and suitable mercury preparations are given by intravenous or intramuscular injection

After entry the mercury tends to accumulate in certain tissues Most is found in the kidneys but smaller amounts pass to the liver spleen intestinal wall heart skeletal muscle lungs and bone

Excretion of the metal is slow and the possibility of cumulative action is great After the intramuscular injection of a single dose it takes up to forty days for 25 to 50 per cent to be excreted Most of the mercury (75 per cent) appears in the urine while the rest (25 per cent) is excreted in the feces Traces are present in all the body fluids Appreciable quantities are found in the saliva

Since the urine is the chief excretory path and large amounts of the

normal animals The wax content of the tubercle bacillus has been extensively studied It apparently resembles beeswax in appearance but is more brittle It is undoubtedly a formidable factor in the viability of this insidious invader

The Metabolism of Bacteria—The metabolism of bacteria is biologically similar to that of other living tissue Bacteria vary in metabolic potentialities *Autotrophic* bacteria utilize simple inorganic sources of nitrogen carbon sulfur and other elements and from them synthesize protoplasm *Heterotrophic types* which require organic substances as sources of carbon and/or nitrogen include all of the bacteria pathogenic for man

The nitrogen requirements of even the most exacting bacteria can be met by amino acid mixtures Most heterotrophes require carbon in the form of hexose sugars although there is considerable latitude in this requirement Bacteria like man also require electrolytes (Na K Fe or Mg) sulfate and phosphate radicals and vitamins Staphylococci need both thiamine and nicotinic acid and some species require biotin as well The influenza bacillus will not grow unless it is supplied with preformed coenzyme I Ordinary laboratory media (infusion broth) enriched with blood or other substances usually contain enough of the essential vitamins to permit bacterial growth

Bacteria carry on *anabolic* functions by which they build food substances into protoplasm and *catabolic* functions in which food and bacterial substances are broken down into simpler end products with the release of energy necessary for the maintenance of the life of the cell The catabolic processes are essentially the mechanisms of bacterial respiration and fundamentally they are similar to the respiration of human cells

Metabolic functions are carried on by a complex system of *enzymes* and *catalysts* Bacterial respiration is essentially a chemical system in which electrons (hydrogen) are passed from one substrate to another with the release of energy during each step The process of hydrogen donation and acceptance requires the mediation of enzymes and catalysts at each step in the process Oxygen which is required at the end of the process to act as the final hydrogen acceptor is obtained in molecular form from the air (facultative anaerobes and aerobes) or as a by product of fermentation reactions carried on by the cells (obligatory anaerobes) One of the respiratory enzymes *cytochrome* is an iron containing pigment closely related to hemoglobin

The study of *bacterial enzyme systems* is as yet in its infancy but it is of great importance since it is a key to the understanding of human cellular physiology and chemotherapy The anti infective agents probably produce their lethal effects on bacteria not by a direct noxious action but by interfering with and blocking certain essential enzymatic reactions in bacterial metabolism

Antigenic Structure of Bacteria—Antigens are substances which when introduced parenterally into the human or animal body stimulate the production of specific *antibodies* capable of uniting with antigens in an observable manner Antigens and antibodies are named according to the reaction observed when they unite under controlled specified conditions Thus when clumping into visible aggregates results from their union the

intestine in the bile but much is reabsorbed Seldom does more than 25 per cent of the total daily excretion appear in the feces The fecal excretion of large amounts of mercury which occurs in cases of mercurial poisoning produces intense irritation of the intestinal mucosa leading to ulcerations and bloody diarrhea

Local Action—On local application mercuric ions are extremely irritating They precipitate protein forming a soluble mercury albuminate which has great penetrating power and is thus corrosive The application of soluble mercury salts to the skin causes dermatitis inflammation vesication and even necrosis

Antiseptic Action—Mercury compounds were among the first used antiseptics The growth of most bacteria is inhibited by a 1 300 000 dilution of mercury bichloride The mercury ion seems to act on bacteria in two stages (1) there is a primary adsorption on the surface of bacterial cells (2) then the organism is killed Substances which can absorb mercury interfere with the action on bacteria and limit the bacteriostatic effect Hence mercury salts are unsuitable for rapid disinfection and are ineffective in the presence of excess protein

The inorganic mercury compounds do not possess a selective action on bacteria and are very irritating to the host They have poor penetrability lose most of their germicidal action in the presence of exudates and are extremely toxic

Certain new organic compounds (merthiolate) are less irritant more penetrating and have a lower toxicity They also have more bactericidal potency than the organic compounds This latter property is not entirely dependent on the liberation of mercuric ions (Hg^{++})

Cathartic Action—Mercurous chloride calomel when taken orally yields a small amount of mercuric oxide (Hg^{++}) in the intestinal tract The mercuric ion being intensely irritating gives rise to increased peristalsis Catharsis occurs within twelve hours after administration

At one time it was thought that mercury in the form of calomel was an excellent *cholagogue* The preparation was widely used in biliousness Recent investigations show that mercury does not cause increase in the flow of bile The stools are green after this drug however because the normal conversion of bilirubin to urobilin which requires bacterial action is interfered with

Diuretic Action—The diuretic action of mercurial compounds is generally regarded as a mild form of toxicity which leads to a depression of tubular reabsorption This allows a greater excretion of water and electrolytes (see *Mercurial Diuretics* p 2261) Large amounts of mercury give rise to necrotizing nephrosis with anuria (see *Mercury Poisoning* p 765)

Antispirochetal Action—Mercury exerts a slow lethal action on spirochetes It is believed to check the growth of the organisms and thus to allow the immune defense mechanisms to overcome and eradicate them The drug to be effective must be given for a long period of time in sufficient quantity to act against the parasites It is often difficult to accomplish this since the effective therapeutic dose often is close to the toxic concentrations

Salivation and Stomatitis—Mercurial medication almost invariably

with differences in colony morphology H colonies tend to spread out in a film on the surface of agar plates whereas O colonies are discrete and isolated H and O variations are independent of S and R An organism may be flagellated (H) or nonflagellated (O) and at the same time either smooth (S) or rough (R)

Practical Significance of Antigenic Fractions—The recognition of the many antigenic fractions of bacteria is of far more than academic interest to the practitioner Upon the demonstration of pneumococcus capsular antigen depends the *typing of pneumococci* necessary for the administration of the correct antisera The performance of the *Widal test* with H and O antigens yields information of value and clears up the confusion resulting from the reporting of positive Widal tests in patients not suffering from typhoid fever Recognition of the fact that *brucella* and *tularemia* organisms have common antigens avoids the diagnostic confusion resulting from positive agglutinins to both in a patient ill with either disease In the preparation of vaccines for active immunization it is necessary to select smooth virulent organisms possessing the full complement of antigens characteristic of the micro organism in question *Pertussis vaccines* at first were ineffective because of failure to recognize this fact It is only in recent years that potent whooping cough vaccines have been made by the careful selection of smooth virulent organisms

The Virulence of Bacteria —An infectious disease is the result of an interaction between host and invader The resistances of the latter are elsewhere described The present concern is the property of bacterial virulence by which the organism overcomes tissue resistance and produces disease

While in general invading bacteria must gain access to and multiply in the tissues of the host organisms such as the diphtheria bacillus remain localized in the mucous membranes and produce distant effects by the liberation of *soluble toxin* Those bacteria which have not the weapon of exotoxin are required to invade the tissues and the blood stream in order to attack the host by the production of *endotoxin* and/or *aggressins*

Exotoxin—One of the most important attributes of many pathogenic bacteria is the ability to produce exotoxins These are soluble protein substances obtained from filtrates of bacterial growth In general they are heat labile being inactivated by a temperature of 70° C or higher They are antigens and capable of stimulating the production of specific *antitoxins* which neutralize them in a quantitative way according to the law of multiple proportions

Exotoxins have definitive pharmacological actions demonstrable even in minute quantities *Tetanus toxin* has a specific action on motor nerve cells *diphtheria toxin* on cardiac muscle adrenal cortex, motor and sensory nerves and *botulinum toxin* on the oculomotor and respiratory nerve cells Specific exotoxins have been demonstrated for diphtheria tetanus botulinum Welch bacillus and other gas gangrene organisms Shiga dysentery hemolytic streptococci and possibly certain strains of staphylococci The claim that other organisms such as meningococcus produce exotoxins is not yet well *substantiated* Snake *venoms and vegetable* poisons (ricin) are pharmacologically and immunologically similar to bacterial exotoxins

Endotoxin—Many bacteria owe a part of their virulence to the effects of endotoxins The nature and properties of these substances are much

3 MERCURIC OXYCYANIDE—This compound is claimed to have a greater antiseptic action than mercuric chloride Its chief advantage is the fact that it does not corrode surgical instruments A 1 1000 solution is used to disinfect catheters bougies etc A 1 5000 solution is used in *ophthalmia neonatorum* and is a good general antiseptic Ampoules containing 8 to 16 mg (⅛ to ¼ grain) in solution are available for intravenous use in the treatment of *syphilis*

4 MERCURIC SALICYLATE—This compound is used by intramuscular injection in the treatment of *syphilis* It is given in doses of 0 065 to 0 1 gm (1 to 1½ grains) suspended in sterile olive or maize oil Aqueous solutions are used locally as antiseptics

5 MERCURIC SUCCINIMIDE—Solutions of this salt are said to be relatively non irritating 0 01 to 0 02 gm (⅙ to ⅓ grain) in a 2.5 per cent aqueous solution is given intramuscularly in the treatment of syphilis

INSOLUBLE MERCURY COMPOUNDS—Metallic mercury and various insoluble salts are used in ointments as antiseptics parasiticides and antisyphilitics These preparations yield a low concentration of ionic mercury but in view of the ointment vehicle are capable of acting for extended periods

1 YELLOW MERCURIC OXIDE OINTMENT contains 1 per cent yellow mercuric oxid in wool fat and petrolatum It is commonly used in the eye in the treatment of *conjunctivitis* and hordeolum and is applied to the skin in epidermophytosis and pediculosis corporis and pubis

2 AMMONIATED MERCURY OINTMENT (U.S.P.) contains 10 per cent of the salt in a lanolin base with white petrolatum and white wax It is a widely used remedy in cutaneous pyogenic infections particularly *impetigo* In children it is safer to use 5 per cent or 3 per cent ointment since the preparation may irritate delicate skins

3 STRONG AND MILD MERCURIAL OINTMENTS (U.S.P.) contain 50 per cent and 30 per cent metallic mercury respectively in a lanolin base with wax and petrolatum These preparations are used chiefly in the treatment of *syphilis* Four gm of the 50 per cent ointment dispensed in waxed paper is the average dose for inunction

4 CALOMEL OINTMENT—Calomel ointment 33⅓ per cent (2 to 4 gm [30 to 60 grains]) is used prophylactically against venereal disease

Insoluble compounds of mercury are given orally in the treatment of syphilis but their use is rapidly falling into disuse The adult dose of *mercuric iodide* is 4 to 8 mg (1/16 to ⅛ grain) *Mercurous iodide* is less soluble and is given in larger doses (15 to 60 mg [¼ to 1 grain])

Mild mercurous chloride (calomel) is relatively insoluble and is a widely used cathartic It acts slowly as a cathartic and is best given in divided doses The average adult dose is 0 125 to 0.3 gm (2¼ to 5 grains) It is incompatible with oxidizing agents (liberating mercuric ion) alkaloids and various gums If active purgation is not induced a saline purge should be given 15 to 18 hours after the last dose An amount of 0 1 gm (1½ grains) suspended in oil is given intramuscularly in the treatment of syphilis

COMPLEX ORGANIC COMPOUNDS—A number of complex organic compounds containing mercury have been introduced in an attempt to avoid toxicity and to utilize the chemotherapeutic actions of mercury to the fullest extent In most instances toxicity has been decreased and chemotherapeutic activity has left much to be desired

1 MERCUROCHROME—Mercurochrome was one of the first of these compounds It is a fluorescein derivative containing 24 to 26 per cent mercury On local application it is bacteriostatic and bactericidal and is free of irritative effects The per cent aqueous solution is a commonly used mild antiseptic The surgical solution of mercurochrome (2 per cent mercurochrome in 5 parts of 0 p r c nt alcohol 10 parts of acetone and 35 parts of water with 0 1 per cent added sodium carbonate) is good for preoperative disinfection of the skin The action of mercurochrome is limited to the surface in which it comes in contact, unless the tissue is

BACTERIAL ECOLOGY (THE NORMAL FLORA)

Bacteria are ubiquitous They are present in air soil water or food stuffs and they thrive in and on all other matter living or dead Bacteria engage in the same struggle for existence as do other living organisms Their associations with other microorganisms may be helpful or noxious In the former instance the relationship is one of synergism whilst a hostile exchange is an antagonism Lesser organisms the *bacteriophages* prey upon bacteria and bacteria in their turn may live upon higher organisms When this co existence occurs without benefit or harm to either structure the state of *commensalism* exists Occasionally bacteria assist the activities of their host and live in a state of *symbiosis* as illustrated by the coliform bacilli in the human bowel

The study of bacterial commensalism and symbiosis is the science of bacterial ecology which is concerned with the mutual relationships between organisms and their environments

Bacterial Ecology and the Practitioner —Bacterial ecology is of importance to the practitioner in order that he may interpret correctly the significance of bacterial findings as reported from the laboratory *Only by recognizing the normal flora of the locality or tissue can he avoid the error of assuming that the isolated organism is necessarily the etiological agent of the disease* The identification of a *Staphylococcus albus* from the skin *does not mean that this bacterium produces acne vulgaris* The growth of a non hemolytic streptococcus from the throat does not necessarily indicate that the patient has a streptococcic sore throat and that intensive chemotherapy is required The *Treponema buccale* is not the cause of syphilis or Vincent s infection and its identification does not justify arseno therapy The smegma bacillus is a normal resident of the genitalia and it is not related to the tubercle bacillus though each is acid fast

These and other important facts require the practitioner to familiarize himself with the normal flora of the body and its orifices

The Flora of the Skin —The bacteria of the normal skin include *Staphylococcus albus* *Staphylococcus aureus* Diphtheroids Mycobacteria (*B smegma*) *B subtilis* a spore bearer *Streptococcus viridans* and non hemolytic streptococci (gamma)

The smegma organism is acid fast and must not be confused with the tubercle bacillus The spore bearing *B subtilis* may resemble *B tetanus* in spreads Vaccines prepared from saprophytic staphylococci can have little or no effect on pyodermas

The Flora of the Normal Mouth —Great numbers of bacteria and other organisms are present in the mouth The commonest varieties are (1) staphylococci chiefly *albus* but also a small number of *aureus* strains (2) *streptococci* green (*alpha*) and anhemolytic or indifferent (3) gram positive bacilli of the *subtilis* variety (4) gram negative bacilli such as *proteus* and *coli* (5) spirochetes of numerous types such as *Treponema buccale dentium* and Vincent s spirillum (6) organisms of the actinomyces group and (7) various types of yeasts

Considering the large amounts of debris and decayed food the many crypts and pockets about the mouth in which bacteria may lodge and find pablum the mouth is ordinarily surprisingly free of infection Most of the organisms are nonpathogenic or of low invasive power In the presence of

Absorption and Excretion—Antimony is never administered orally unless a nauseant or expectorant effect is desired The organic compounds are rapidly absorbed after intramuscular injection They are in turn excreted rapidly in the urine Most of the antimony is eliminated within three days

Preparations ANTIMONY AND POTASSIUM TARTRATE (U.S.P., B P)—This is a white granular powder (or colorless odorless transparent crystals) with a sweet taste It is water soluble (1 12) contains trivalent antimony and is dispensed in ampoules for intravenous use or in crystalline form After intravenous administration the drug may produce a marked fall in blood pressure which is probably due to a direct action on the peripheral arterioles and cardiac muscle Usually injection causes coughing which is not a sign of danger

The average adult dose in the treatment of *trypanosomiasis schistosomiasis kala azar* and *granuloma inguinale* varies from 30 to 130 mg every alternate day

ANTIMONY SODIUM THIOGLYCOLLATE N N.R—This is an organic compound containing not less than 37 per cent trivalent antimony It is a whitish pinkish powder with a faint odor and is very soluble in water

From 0 05 to 0 1 gm dissolved in 10 to 20 cc of sterile water are given every three to four days in courses of 20 to 25 intramuscular injections

This compound is less toxic than antimony and potassium tartrate and is useful in the treatment of *granuloma inguinale lymphogranuloma venereum kala azar* and *filariasis*

FUADIN N N R—Fuadin or stibophen contains 13 6 per cent of trivalent antimony It is supplied only in an approximately 6 3 per cent solution (Each cc contains 8.5 mg of antimony)

The drug is given intramuscularly in gradually increasing dosage On the first day one gives 1.5 cc on the second 3.5 cc on the third fifth seventh ninth eleventh thirteenth and fifteenth days 5 cc are given the total being 40 cc of the 6.3 per cent solution The course may be repeated after a rest period of one to two weeks Then the drug is given once a week and then every two weeks for several weeks to prevent relapses

Fuadin is one of the better known derivatives of antimony and is particularly valuable in *granuloma inguinale* and *schistosomiasis* In the latter disease iron salts are given between courses of fuadin

UREA STIBAMINE—This is an organic compound derived from phenyl stibinic acid which contains antimony in pentavalent form The drug is given intravenously and is the preparation of choice in the treatment of *kala azar* (Snapper) Injections may be attended by epistaxis nausea palpitation substernal oppression and skin rashes The occurrence of a slight reaction after one injection is an indication for the reduction of subsequent dosage to prevent a lethal vasomotor collapse The use of antimony has reduced the mortality from kala azar almost 90 per cent (p 535)

MISCELLANY—A number of other antimony preparations are used by various nationalities in the treatment of tropical diseases in their dominions These include *stibamine isethionate stibamine glucoside neo antimosan neostam neostibosan* (Bayer 693) and *solustibosan* (Bayer 461)

pneumonia The presence of "pneumococci' in the throat is meaningless unless the type is also indicated The bacteriological diagnosis of pneumonia should never be made on the basis of a throat culture if it is possible to obtain sputum Sputum is unobtainable only in the case of infants and young children *Grievous errors in typing can be made by assuming that the pneumococci present in the pharynx are necessarily responsible for pneumonia in the patient* This is particularly true of Type III pneumococcus which is present in the pharynx of 10 per cent of normal persons If such a Type III carrier develops pneumonia and the bacteriological diagnosis is attempted from a throat culture errors are inevitable Type III organisms may be present in the throat culture and Type I in the sputum or blood culture

Influenza bacillus (Pfeiffer s bacillus) is a common inhabitant of the pharynx This organism despite its name has no etiological relation to *influenza which is a virus disease The influenza bacillus however may* produce an acute catarrhal inflammation of the pharynx and larynx in young infants and is also the cause of a highly malignant type of meningitis In older children and adults its presence in the throat is usually of no significance

The diphtheroids normally present in the nasopharynx are of no importance except that they may be confused with true diphtheria organisms Whenever diphtheria is suspected smears and cultures should be examined by the expert If diphtheria bacilli are found it should be remembered that about 1 per cent of healthy persons are ' carriers hence the organism should be tested for virulence Naturally the administration of antitoxin does not wait on these bacteriological refinements Specific therapy is instituted on the basis of the clinical suspicion

The Vincent spirochetes and fusiform bacilli are also common inhabitants of the normal pharynx and mouth They should be accepted as the etiologic agents of disease only if present in large numbers and if the clinical condition resembles Vincent's infection (ulceromembranous)

The Flora of the Gastro intestinal Tract *In the Newborn*—The bowel is sterile at birth but soon becomes contaminated with organisms introduced through the mouth and rectum The intestinal flora of the breast fed infant is relatively simple consisting largely of *Lactobacillus bifidus* In the bottle fed infant the predominating organism is *Lactobacillus acidophilus* and other organisms commonly found include coliform bacilli enterococci gram positive aerobic and anaerobic spore bearing bacilli

In the Adult—In the adult, the empty stomach is generally sterile Organisms ingested with food swallowed in the saliva are rapidly killed by the acidity of the gastric juices with the exception of spores and some acid resisting bacilli Botulism toxin and perhaps staphylococcus enterotoxin are the only bacterial toxins which resist destruction by the digestive enzymes If the acidity of the stomach juices is reduced or the motility of the organ excessive the sterilizing action may be incomplete or lacking Thus in cases of *gastric carcinoma many saprophytic organisms may remain* or actually multiply in the stomach The tubercle bacillus resists destruction by the gastric juice and hence gastric aspiration is a valuable method of recovering and demonstrating the organism in cases of suspected pulmonary tuberculosis with scanty or absent sputum (p 2190)

The *collargol type* contains 78 per cent metallic silver reduced to colloidal form by chemical means and stabilized by a small percentage of egg albumin (denatured). It is used mainly for intravenous or intramuscular injection. The possibility of an allergic action to egg must be borne in mind in sensitive individuals.

The *electric type* consists of colloidal solutions of metallic silver that are prepared electrically. These solutions are dilute and unstable.

TABLE 17.—USES AND DOSES OF PROTEIN SILVER

	Strong Protein Silver Per cent	Mild Protein Silver Per cent
Eye		
Conjunctivitis, simple, purulent or gonorrheal	2 to 10	Solutions 25 Ointment 10
Prophylaxis against ophthalmia neonatorum	2 to 10	25
Prophylaxis before ophthalmic operations (several days)		25
Corneal ulcers		50
Nose and throat	0.5 to 10	Spray 10 to 20 Swab 25 to 50
Wounds and ulcers		1 to 10 solution or ointment 10 dusting powder
Gonorrhea		
Injections—Prophylactic	2	10
Acute	½ to 1	5 to 10
Chronic	2 to 10	10 to 20
Urethral irrigation	1:2000 to 1:1000	1:1000
Urethral suppositories	5 to 10	20 (0.13 gm. or 2 grains)
Cystitis		20 to 50 (5 cc.) or 10 to 25 (30 cc.) left in bladder
Gynecologic Practice		
Solutions	2 to 10	25 (tampons of solution in glycerin)
Tampons	2	—
Ointments	5	—
Suppositories	5	20 (0.3 gm. or 5 grains)
Rectal Administration		
Irrigation	0.1	0.1 to 1
Injection	5	10
Suppositories	5 to 10	20 (0.13 gm. or 2 grains)

From New and Nonofficial Remedies, 1941.

The *silver halide type* contains mixtures of colloidal silver salts in suitable diluents. They are nonirritant, nonastringent and are colorless.

LUNOSOL.—Lunosol contains 10 per cent colloidal silver chloride, sucrose 89 per cent and sodium chloride 1 per cent. This preparation is used in 1 to 25 per cent solutions for irrigation of the urethra, vagina and rectum. Solutions of 25 to 50 per cent are used in the eye.

NEO SILVOL.—Neo Silvol is a compound of silver iodide with a soluble gelatin base containing 18 to 22 per cent colloidal silver iodide. Solutions tend to precipitate gradually after standing longer than a week.

pairs are present and they must be carefully distinguished from gonococci

Female Urethra and Vulva—The female urethra is usually sterile but may contain a few harmless saprophytes In both sexes smegma bacilli are present in the preputial secretions or about the vulva These organisms are acid fast and morphologically resemble tubercle bacilli Occasionally they get into urine leading to the unwarranted suspicion of renal tuberculosis The vulva also harbors staphylococci diphtheroids coliform organisms enterococci yeasts and anaerobes most of which are saprophytes

Vagina—The normal vagina flora varies with the *p*H of the secretions Before puberty the vaginal secretions are alkaline and the commonly present organisms include staphylococci green or indifferent streptococci and enterococci coliform bacilli and diphtheroids

After puberty, the secretions become acid The predominating organism is then the Doderlein s bacillus a fairly large gram positive rod belonging to the group of lactobacilli and entirely non pathogenic Anaerobic streptococci are also normally present in the adult vagina These organisms are non pathogenic in the vagina but if they gain access to the uterus or surrounding tissues during parturition they may be the cause of puerperal sepsis Hemolytic streptococci are normally not present in the vagina *Trichomonas vaginalis* is not a normal inhabitant of the vagina but is commonly found in the presence of leukorrhea and vaginitis

The Flora of the Eye—Many types of bacteria may occasionally occur on the normal conjunctiva but *Corynebacterium xerosis* and *Staphylococcus albus* are the only inhabitants to be found with any degree of constancy In smears the former are present in considerable quantity while the saprophytic staphylococci are generally sparsely represented

The finding of numerous staphylococci in smears suggests pathogenicity and while certain pathogenic bacteria such as the *pneumococci Staphylococcus aureus streptococci influenza bacilli* and *colon bacilli* also may be present on the conjunctiva without inducing symptoms they must be considered pathogenic if they are found in large numbers in patients with conjunctivitis Bacteria such as *gonococci* the *Koch Weeks bacillus* and the *diplobacillus of Morax Axenfeld* are so seldom found on the normal conjunctiva that their demonstration must always be assumed to indicate pathogenicity

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Gynecologic Practice		
Solutions	2 to 10	25 (tampons of solution in glycerin)
Tampons	2	—
Ointments	[illegible]	—
Suppositories	[illegible]	20 (0 3 gm or 5 grains)
Rectal Administration		
Irrigation	0 1	0 1 to 1
Injection	2	10
Suppositories	5 to 10	20 (0 13 gm or 2 grains)

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Virulence—The perfection of a method to differentiate virulent from nonvirulent staphylococci would be highly useful to the clinician To accomplish this many attempts have been made to separate *antigenic fractions* A nucleoprotein moiety has been obtained but this is only species-specific Julianelle classified the organisms by virtue of their specific carbohydrates into an *A* or *pathogenic variety* and a *B* or *nonpathogenic variety* Very young cultures of staphylococci sometimes appear to be somewhat encapsulated and these capsules probably correspond to the soluble specific carbohydrate described by Julianelle At present however no classification of staphylococci based on soluble specific substance can be used for routine practice

Pigment production furnishes some indication of pathogenicity since the *aureus* variety is the more likely to be invasive On the basis of large numbers of observations certain somewhat arbitrary criteria have been established In general *Staphylococcus aureus* especially the hemolytic variety may be regarded as pathogenic whereas *Staphylococcus albus* is usually nonpathogenic or associated with mild infections such as stitch abscesses The pathogenic staphylococcus should coagulate plasma, ferment mannite and cause hemolysis of sheep cells Pathogenic strains should also be lethal to laboratory animals particularly rabbits when injected intravenously

The fact that an organism fulfills the laboratory criteria of a virulent strain does not in itself prove that it is responsible for clinical disease Pathogenic staphylococci may be cultured from normal throats and even from the normal skin Staphylococci are likely to be of etiological significance when they are obtained from lesions in pure culture or as the predominant organisms

The laboratory criteria of virulence are by no means absolute since invasiveness depends upon factors of resistance in the host also When the clinical manifestations point to infection with an organism of supposedly low or no virulence this information may be employed prognostically since it implies that the tissue resistance of the host is diminished to a point where the bodily defenses are all but impotent

Immunity—The immunity to staphylococcal disease is cellular rather than humoral The frequency of staphylococcal disease and its tendency to affect all ages from infancy to the aged indicate that for the most part, *there is little significant natural or acquired immunity* On the other hand the regular presence of staphylococci on the skin and mucous membranes and their frequent entrance into the superficial tissues without the production of notable infection indicates that the intact healthy tissues form a natural barrier against invasion and that there must be a potent local tissue resistance under ordinary circumstances

The *mechanism of recovery* from staphylococcal infection is presumably dependent upon phagocytosis or tissue resistance While antitoxin and opsonin can be demonstrated in variable amounts in the blood these substances may be present in normal persons as well as those suffering with or convalescent from staphylococcal infections There is little clear evidence therefore that these antibodies are of importance in recovery from clinical infection

Pathology—The essential pathologic feature of staphylococcal infection is the *abscess* which consists of an area of central liquefaction necrosis containing staphylococci polymorphonuclear leukocytes (alive or dead) and variable amounts of cellular debris Surrounding the central necrotic area is an inflammatory zone characterized by the presence of polymorphonuclear leukocytes hyperemic capillaries distended lymphatics and edema of the interstitial tissue The nature of this localized lesion is partially explained by the action of leukocidin necrotizing substance and coagulase

If the defense reaction is favorable the necrotic material eventually reaches the body surface pus is discharged and the lesion as a whole proceeds to healing If there has been additional trauma rough handling or excessively early surgical intervention the lymphatics and capillaries adjacent to the abscess may be opened permitting the dissemination of organisms into the blood stream Perhaps this process is aided by the spreading factor The lethal element adds to the general toxemia that is exhibited by the patient

Epidemiology—Of the staphylococcal infections only *impetigo of the newborn* (p 305) constitutes a public health menace Particularly in institutions this affliction may sweep a nursery and result in the death of an appreciable percentage of the affected infants Impetigo of the newborn is a reportable disease and public health authorities should be requested to cooperate in its control

CLINICAL MANIFESTATIONS

Infections caused by staphylococci are very common They vary in severity from trivial furuncles to fatal septicemia

CHAPTER 3

BACTERIAL INFECTION GENERAL CONSIDERATIONS

Bacteria
Bacterial Ecology (The Normal Flora)

BACTERIA

BACTERIA are minute unicellular plant like organisms without chlorophyl (Zinsser)

Size and Form —Bacteria are among the smallest of all living organisms It would require a colony of 250 000 bacteria of average size to cover the head of a pin Magnification with the oil immersion lens of the ordinary microscope brings bacteria well within the range of visibility Bacteria vary in size from more than 10 microns to less than 1 0 micron in the greatest diameter whereas by comparison the average red blood corpuscle is 7 to 8 μ in diameter Each micron (μ) is $\frac{1}{1\,000\,000}$ meter

Bacteria commonly occur in three main morphological forms the cocci or spheres the bacilli or straight rods and the spirilla or curved rod forms

Cocci are usually perfectly spherical When two cells are in close contact they become biscuit shaped or flattened along the opposing surfaces (gonococci) They may also appear in grape-like clusters (staphylococci) or chains (streptococci) Cocci do not develop spores or flagella and are non motile They may become encapsulated (pneumococci)

Bacilli may be short and thick or long and slender They may show considerable pleomorphism with short thick forms and long filaments present in the same smear Some possess capsules (*Bacillus mucosus capsulatus*) and others contain *polar* bodies (*C diphtheriae*) or spores (*B tetani*) which may be centrally placed or located at the poles Some bacilli are capable of active motion through the possession of flagella (typhoid bacillus) These whip-like structures may be single or arranged in tufts at one or both poles or completely surrounding the bacterial body

Some bacteria assume the form of *spirilla* (the comma shaped vibrio of cholera)

Morphology of Bacterial Cell —Unstained bacteria are transparent and colorless possessing a delicate *cell membrane* which constitutes a first line of defense against the counterattack of the host and his medical attendant

Some organisms notably the tubercle bacillus possess a waxy and almost impenetrable casing and many bacteria possibly most of them posse s capsules In some cases (pneumococcus Friedlander s bacillus) the capsules are large and easily seen whereas in other instances special staining procedures are required for their demonstration In pneumococci Friedlander's bacilli influenza bacilli and meningococci the *antigenic structure* of the capsule varies for different types within the group This fact is utilized in serodiagnosis in the *Neufeld or quellung reaction* (p 201)

In general *encapsulated organisms* are more virulent than non-capsulated members of the same strain The reason for this will be discussed

recognized by *Gram stains* of the local exudate or by *cultures* on ordinary media

The demonstration of a staphylococcal bacteremia requires simple media and growth is usually obtained after twenty four to forty eight hours incubation Little or no additional information is afforded by serologic tests and indeed none is required

Local Treatment with Anti infective Agents

Staphylococcic skin infections are benefited by the local application of the anti infective agents Accessible lesions may be treated with 1 per cent *gentian violet* 5 per cent *sulfathiazole cream* 0 04 per cent *tyrothricin* (p 104) or a solution of *penicillin* in a concentration of 250 to 10 000 units to the cubic centimeter No one of these preparations is of any value unless it comes into direct contact with the bacteria Gentian violet is objectionable because of the discoloration the sulfonamides are inhibited by pus dead bacteria and procaine solution and have the additional disadvantage that they may cause toxicologic manifestations and sensitization (p 99) tyrothricin preparations may be hemolytic even when applied to the surface Only penicillin has unmodified potential for good and relatively none for ill

Systemic Treatment with the Anti infective Agents

The systemic use of the anti infective agents is mandatory in the presence of staphylococcemia metastatic infections significant secondary infections and primary staphylococcic lesions in which there is evidence of absorption The use of these preparations is futile in a staphylococcic food poisoning their administration is optional in the local pyodermas unless they are generalized persistent or recurrent

For specific anti infective treatment the practitioner has his choice of *sulfonamide* or *penicillin* If the patient is ambulatory the former must be employed and the choice of preparations rests between *sulfadiazine* and *sulfathiazole* Our preference is for sulfadiazine on the ground that it has powerful antibacterial effect minimum toxicologic potentiality and can be administered for a long span of time in large dosage with little risk For a mild to moderate infection the initial dose may be 2 to 4 gm (30 to 60 grains) with 0 5 to 1 0 gm (7½ to 15 grains) at four six or eight hour intervals depending upon the response In patients who are more seriously ill and who require a higher concentration the initial dose may be 4 to 6 gm (60 to 90 grains) with 1 gm (15 grains) at four hour intervals day and night until a satisfactory outcome has been assured

The treatment of the patient who is confined to bed may be effectively accomplished by the use of sulfonamide penicillin or both agencies in combination We prefer to rely upon *penicillin* alone because of its minimum toxicity The initial dose given intramuscularly may be 50 000 to 100 000 units dissolved in 2 to 4 cc of sterile distilled water saline solution or dextrose with three-hourly repetitions of 25 000 to 50 000 units day and night until the clinical situation is well under control Exceptions to this routine of therapy are encountered in an intense staphylococcemia and in a staphylococcic meningitis In the first instance where each minute counts an intravenous drip is set up and after the priming dose of 50 000 to 100 000 units an infusate may be prepared so that each cubic centimeter contains 250 or

Besides binary fission other modes of asexual reproduction have been described These include for example *lateral budding* and *branching* Sexual modes of reproduction may result from the conjugation of two or more individuals and there is evidence that some organisms particularly those of the pleuropneumonia group have a complicated life cycle Claims of a bacterial life cycle have been made also for the tubercle bacillus but these are not generally accepted

Rate of Bacterial Growth —Under suitable conditions the rate of bacterial growth is unbelievably rapid Cell division may be accomplished every twenty to thirty minutes depending upon incubation temperature and cultural conditions Unimpeded at this rate as many as 1 000 000 organisms occupying a space of approximately 1 cu mm might be produced at the end of fifteen hours Were this rate of multiplication to be continued for twenty four hours sufficient bacterial bodies might be produced to fill an ordinary egg-cup At the end of thirty six hours the progeny of a single cell might occupy a space of 1000 cubic meters[1]

Fortunately for mankind the curve of bacterial growth is not a simple geometric progression In terms of the number of viable organisms per unit volume of medium a graph of the bacterial population of a culture tube reveals (1) *An initial stationary period* (lag phase) lasting two to three hours (2) *a period of accelerating multiplication* (physiological youth) lasting three to five hours (3) *a phase of decreasing rate of growth* (4) *a stationary epoch* (5) *a period of decline* or accelerating death rate lasting perhaps ten hours and restoring the total count of viable organisms to the number estimated during the period of physiological youth (6) *a period of accelerated maximum death rate* and (7) *total dissolution*

There is evidence to suggest that the anti infective agents such as sulfonamide and penicillin inhibit bacterial multiplication Were this a veritable fact the span of infectivity could only extend through the life of a single generation of micro organisms after which the host defenses would prevail as suggested clinically

Bacterial Colonies —When bacterial multiplication has reached the point where macroscopic evidences of growth are clearly visible on the surface of solid media the bacterial mass is spoken of as a colony The sizes and shapes of bacterial colonies vary with the conditions of incubation and the character of the medium but in general they are distinctive enough so that many species can be recognized by their colonial morphologic appearance Some organisms produce characteristically *pigmented colonies* as for example *Staphylococcus aureus* Others produce changes in the surrounding medium such as the *green ring* of methemoglobin around colonies of pneumococci or alpha streptococci on blood agar plates Hemolytic streptococci effect a *clear zone of hemolysis* on blood plates *Bacillus mucosus capsulatus* (Friedlander bacillus) *B aerogenes* and pneumococcus Type III form large *mucoid colonies* which are quite typical and easily recognized others such as the influenza bacillus produce clear *dew-drop* colonies which may be iridescent while others (tubercle bacillus) grow in dry *crenated* colonies The experienced bacteriologist can identify many common organisms with considerable accuracy by the morphologic appearance of the colonies on the surface of solid media

The anti staphylococcic therapeutic armamentarium is so rich and powerful that the practitioner must never abandon hope of a successful issue All else failing streptomycin therapy may be used for an organism insensitive to other antibiotics (p 103)

Nonspecific Treatment

The extraordinary efficacy of chemotherapy in staphylococcal infection must not lead to neglect of the nonspecific measures of therapy that include surgical interference The areas of local lesions are to be handled with scrupulous *cleanliness* and *avoidance of trauma* Unless pain is excessive the sites should be scrubbed with soap and water and protected by sterile dressings Trauma particularly is avoided as for example the wearing of stiff collars and tight neckbands in men who suffer from furuncles or carbuncles of the neck Males with facial lesions should avoid shaving *Under no circumstances should dressings be fixed with adhesive plaster* In overwhelming protracted or seemingly resistant infection especially in the weakened the aged and the very young high concentrations of penicillin effected by massive daily dosages of 500 000 to 1 000 000 units or by the production of blockade (p 109) are worthy of earnest consideration

The effects of *local heat* on the pyoderms cannot be overestimated It has always seemed that bulky *hot wet dressings* of saline solution or boric acid favor localization of the process and early softening preparatory to surgical intervention If it is too burdensome to apply wet dressings dry heat may be used in the form of the electric pad the hot water bag or the infra red lamp Roentgen therapy favors resolution of lesions such as carbuncles

Nonspecific therapy is also directed at *increasing the resistance of the host* The urine of the patient suffering from a staphylococcic infection should be examined particularly for the presence of sugar *Glycosuria* and *hyperglycemia* are to be corrected by dietotherapy (p 669) or the injection of adequate dosages of insulin (p 1237) Debilitated patients and those who suffer an anemia improve on *transfusions* of citrated blood

Surgery

The role of surgery in staphylococcal infection must not be underrated Primary purulent foci must be *drained* An accessible infected vein wall must be *widely excised* Metastatic foci particularly in the accessible deep structures such as the cortex of the kidney require *evacuation* if chemotherapy is to be of any value Staphylococcal osteomyelitis is particularly resistant and usually necessitates surgical procedure

The practitioner will recall that excision and incision of infected tissue hold both promise and threat A premature extensive incision may open up the tissue spaces and invite systemic introduction of infected material So too will the dangerous habit of squeezing boils It is essential for the surgeon to delay his procedure until the abscess has been well walled-off and the contents are liquefied Under these conditions all that is needed is a *minimal incision* to release the creamy or liquid pus There is no doubt but that patients suffer fewer recurrences and experience more rapid healing if the boil is permitted to burst spontaneously without any surgical interference

Sporulation —In certain species of bacteria the periods of accelerating death rate and total dissolution are modified by the ability of the organ ism to sporulate When living conditions become unsatisfactory for the species the spore thickens The remainder of the cell eventually disappears leaving the spore isolated

Spores are highly resistant to heat disinfection and drying They serve to tide the organism over a period unfavorable for growth and may remain viable for longer than ten years (tetanus) When suitable environmental conditions return the spore germinates and the cell reverts to the familiar vegetative form

The successful extermination of spore bearing bacteria is accomplished by producing conditions favorable to the germination of the organism and then rapidly applying the methods of sterilization before sporulation can be resumed

Variability of Bacteria —While constancy in the nature of bacteria is the rule there are convincing evidences that variability in bacterial growth is encountered Alterations in environmental conditions produce *sporulation* and *pleomorphism* Mutation to another species has been described but there is no evidence that this occurs under natural conditions

Microbic Dissociation—Within a given species dissociation or *phase variation* is a common if not universal characteristic of bacteria Cultural methods reveal that bacteria may grow in a *mucoid* or 'M type a *smooth* or S type a *rough* or R type and a G type That this phenomenon is not strictly of academic importance is illustrated in certain species by the virulence of the smooth type and the relative nonvirulence of the rough type

Alterations in form and virulence are suggested as an explanation for *cyclic variations* in the frequency and severity of infectious diseases They suggest possible variants in the intensity of the individual infection in mechanisms of recovery and renewed invasiveness

The Chemistry of Bacteria —Despite laudable and painstaking researches into the chemical composition of bacteria little practical information is available for the practitioner The chemical composition of bacterial proto plasm does not differ essentially from the protoplasm of other living cells The water content varies between 75 and 85 per cent bacteria are some what denser (have less water) than higher plant or animal cells The solids are made up for the most part of protein and carbohydrate with traces of fat The inorganic ash contains the common anions and cations The nitrogen content averages about 10 per cent and the carbon per centage approximates 50 per cent of the dried weight Bacterial proto plasm is rich in nucleoprotein and also contains globulins and possibly albumin A substance resembling the *Bence Jones protein* has been ex tracted from tubercle bacilli Bacterial proteins yield most of the familiar amino acids

Bacteria contain simple sugars polysaccharides starch and glycogen Some of the polysaccharides are either antigens or haptens and are located on or near the surface of the cell giving *type specificity* (pneumo coccus) or *group specificity* (hemolytic streptococcus) Fats lipoids and waxes may be extracted from bacteria Phthioic acid obtained from the tubercle bacillus causes the formation of tubercles when injected into

On the surface of blood agar plates streptococci form small round white opaque colonies Smooth and rough variants (q v) are recognized In the case of the streptococcus the smooth (virulent) organism forms a matte colony which has a rough surface in the literal sense of the term whereas the rough organisms (avirulent) form smooth colonies This confusing situation which is also true for the anthrax bacillus emphasizes the need for a clearer definition of the terms rough and smooth as applied to the virulence of micro-organisms

Classification—Many attempts have been made to separate and classify streptococci on the basis of their capacity to produce disease An early and simple method relied on morphological data Organisms cultured from the normal pharynx or from subacute oral lesions generally grow in short chains whereas those found in acutely inflamed throats in scarlet fever and puerperal sepsis appear in long chains This distinction is useful but, unfortunately not fundamental since it depends in large part on the environmental conditions of growth and the age of the culture

ALPHA BETA AND GAMMA STREPTOCOCCI—The morphological classification has been supplemented by the reactions of the organisms when grown on the surface of blood agar plates Some streptococci have the property of *hemolyzing* completely the red cells surrounding the bacterial colony leaving a clear transparent zone around the growth These streptococci are occasionally grown from apparently normal tissues but more often are isolated from patients with scarlet fever septic sore throat and other infections From their capacity to produce complete or beta hemolysis these bacteria have been classified as *beta hemolytic streptococci* and are recognized as potential pathogens

In contrast to the hemolytic type other streptococci isolated from the normal mouth or from the gums about infected teeth produce partial hemolysis of the red cells convertin the hemoglobin to greenish methemoglobin This so-called *alpha* type of *hemolysis* characterizes the *Streptococcus viridans* which is ordinarily harmless Still other streptococci commonly found in feces have no hemolytic effect and these constitute the *gamma* or indifferent streptococci which are rarely pathogenic

Unfortunately the classification relative to the reactions on blood plates is not of absolute differential value The type of hemolysis produced is not always clearcut The same organism at one time may be beta hemolytic and at another time only weakly hemolytic or frankly green The hemolytic reaction varies with the medium used with the length of incubation and with the temperature and oxygen content of the cultural environment The presence of considerable amounts of sugar in the medium inhibits hemolysis The type of blood used is of some importance better hemolysis occurring with rabbit and sheep blood than horse blood although the latter can be used Hemolysis is most marked after twenty four hours and is often enhanced by growth of the organisms at 37 C for eighteen to twenty four hours followed by storage of the cultures in the refrigerator for another twenty four hours Colonies beneath the surface in pour plates are often more frankly hemolytic than surface colonies

Further attempts to classify streptococci have utilized the study of *metabolic* differences among strains The bacteria have been differentiated by sugar fermention the *p*H of the medium after growth their varying ability to grow in the presence of concentrated salt or strong bile solution and their resistance to heat In general these criteria have been rewarded by the demonstration of a considerable degree of parallelism between metabolic differences and antigenic properties Thus among the beta hemolytic streptococci the *Group A strains* which are exclusively of human origin differ antigenically from the *Group B strains* of bovine origin and also in their varying ability to ferment sugars in the final *p*H attained in broth cultures and in their ability to produce pigment *Group D strains* the streptococci found in human feces generally are able to resist destruction by heating at 60 C for thirty minutes they grow freely in strong bile solutions and have other special characteristics

ANTIGENIC STRUCTURE OF BETA HEMOLYTIC STREPTOCOCCI—The modern classification of beta hemolytic streptococci is dependent upon the analysis of the *antigenic structure* of the organisms The body of the streptococcus contains a nucleoprotein P substance similar for alpha and beta streptococci and for pneumococci and hence of no value in the further separation of these organisms Beta hemolytic streptococci, in addition contain a polysaccharide C substance which is not to be confused with the entirely different C substance of pneumococci By means of a precipitin test beta hemolytic streptococci can be divided into a number of groups according to the kind of C substance which they con

antigen is called an *agglutinogen* and the antibody an *agglutinin* when both are in soluble form the result is a *precipitate* and the reacting members are called *precipitinogen* and *precipitin* respectively

Antigens differ widely in chemical structure and need not necessarily be protein in nature They may be complete or partial The latter (haptenes) are substances which do not have the ability to stimulate the production of antibodies but which nevertheless by virtue of chemical specificity are able *to unite with them*

The Mosaic of Antigens.—Bacteria contain a mosaic of antigens as would be expected from the complexity of their chemical structure The organisms as a whole are antigenic and various fractions of them obtained by chemical or mechanical separation are also complete or partial antigens If they secrete *exotoxins* these too are antigenic Not only the body of the organism but such appendages as *flagella* and the covering *capsule* contain antigens

Cross Reactions from Nonspecific Antigens—The bodies of bacteria contain *nucleoproteins* which appear to have broad chemical relationships in many different species As a result antibodies against the bacterial proteins of one organism may produce a *cross reaction* with those of a number of other species Thus pneumococci of all types have the same body protein which cross reacts with green and hemolytic streptococci that also have a closely related body protein These relatively nonspecific antigens are thought to be located deep within the cell

Capsular and Somatic Antigens—As a general rule the antigenic reactivity of the organism depends mostly on the nature of the surface antigens Hence the body proteins are not important as antigens unless the capsular or other surface antigens have been removed leaving the organisms rough In smooth organisms there are present one or more antigens on the surface which are highly specific for one type or group of bacteria (pneumococci hemolytic streptococci) or for one type within the group (i e Type I Type II etc pneumococcus) These *surface antigens* may be located within easily demonstrated capsules (pneumococci) but are also present on the surface of nonencapsulated organisms (typhoid)

The distinction of smooth and rough (S and R) is of fundamental importance since these varieties of the same organism differ widely in their virulence Organisms freshly isolated from human disease are generally smooth and on prolonged laboratory cultivation they become rough Whether rough forms present as harmless inhabitants on human body surfaces and mucous membranes can spontaneously become smooth and virulent is doubtful There is no evidence that this occurs in nature but it has been suggested as an explanation for periodic variations in the virulence of disease and in the waxing and waning of epidemics Better explanation of these phenomena however lies in the study of variations in human immunity or resistance to disease

Flagellar Antigens—In addition to the capsular and somatic antigens which are associated with S and R variations in bacteria flagellar antigens exist Many bacteria particularly the gram negative organisms which produce enteric disease (Salmonella) have flagella which are antigenic (H antigens) When these organisms appear in nonflagellar form they then have *O antigens* on their surface H and O variations are also correlated

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less clearly defined than the exotoxins In general they cannot be isolated free from bacterial proteins They are probably in large part various fractions of the bacterial bodies liberated mechanically chemically or by autolysis of the organisms They are in general heat stable and produce antibodies which react with the whole bacterial organisms or with chemical fractions of them They do not have specific pharmacological effects and must be injected in relatively large quantities to produce the death of experimental animals

Aggressins—In addition to toxins bacteria exhibit a variety of activities which may or may not be the result of specific chemical entities and which in their net effect interfere with the defense reactions of the host At one time the term aggressin was used to indicate this action in a sense implying that it was the result of a specific substance It is now recognized that the aggressive action of bacteria is the result of many different aggressins' One of the most important of these is *leukocidin* present in staphylococci hemolytic streptococci and many other bacteria It has the property of destroying polymorphonuclear leukocytes thus removing one of the chief bulwarks of the host s defense system *Fibrinolysin* found in hemolytic streptococci has the property of dissolving fibrin clots and aiding in the dispersion of the organism throughout the tissues This substance is antigenic and its presence (as well as antifibrinolysins developed by the resisting host) may be detected by a simple laboratory technic *Coagulase* present in pathogenic staphylococci is a substance which clots plasma *Hemolysins* which destroy red blood cells are present in staphylococci streptococci some strains of diphtheria bacilli some clostridia and other organisms Another important type of aggressin is the so-called *spreading factor* which appears to be identical with hyaluronidase and has the property of enhancing the spread of organisms through the tissues So far it has been isolated from hemolytic streptococci staphylococci and Welch bacilli

In the present sense of the term the *capsular polysaccharides* of pneumococci and *H influenzae* are aggressins These soluble materials diffuse into the tissues and body fluids uniting with and neutralizing specific antibodies thereby protecting the bacteria themselves from the effects of the host s humoral antibodies The virulence of smooth pneumococci is explained in part by this fact The aggressins also include the many *bacterial digestive enzymes* These may continue to function even after lysis of the organisms attacking and breaking down the tissues of the host The *proteolytic enzymes* of certain clostridia are examples of this type of aggressive action of bacteria

All pathogenic bacteria of course do not possess a complete armamentarium of offensive weapons *Botulism* is an example of a pure toxemia It is doubtful if the organism itself has any invasive qualities *Tetanus bacillus* also has almost no invasive properties but is implanted mechanically in the tissue and only produces toxin if the local environment is suitable *Diphtheria* has invasive properties somewhat greater than tetanus but produces disease essentially by the release of toxin *Typhoid* is highly invasive causing septicemia but does not form true exotoxins *Hemolytic streptococci* are highly virulent because they produce true toxins and al o have almost all of the aggressive properties listed above

TABLE 18 —SEROLOGICAL AND BIOCHEMICAL CLASSIFICATION OF HEMOLYTIC STREPTOCOCCI

SEROLOGICAL G OUP	CH EF HABITAT	DI E	HEMOLYS S ON BLOOD AGAR PLATE	STR PTOLYSIN O	FIBRINOLYSIN	FERMENTATION OF		RESIST ANCE TO HEATING A 60 C OR 30 MINUTES	GROWTH ON 10% BILE BLOOD GAR	REDUCTION OF METHYLENE UE IN MILK	FIN L pH IN EX T SE BROTH	SO IUM HI PURATE HY ROLYSIS
						TREHA LOSE	SO BITOL					
A	man	l t f er ts so e throat ery pel p er pe l p i te	+	+	+	+	−	−	−	−	4 8–6 0	−
B	c ttle	bo e mastit s	±	−	−	+	−	−	+	−	4 2 4 8	+
C h m n	m	m ld p rpe al nd uri ary nfect on e p r t ry fe t (of tal case report d)	+	+	+	+	−	−	−	−	4 8–5 4	−
C an mal *py gen s*	horse cattle m t l bo t ry a d do e t c n mals	tr ngles	+	−	−	−	+	−	−	−	4 6–5 0	−
D	(leese) d h m n i test n l tract	occas lly pathogen c fo m	vari bl	0	−	+	+	+	+	+	4 0–4 5	±
E	n m l m lk	n path ge c		0	−	+	+				4 6–5 8	−
F	m n	m ld re p t y infec t s	+	?	−	±	−	−	−	−	4 6–5 4	±
G mal"	cattle d g mo key		+	−	−	+	−	−	−	−	4 6–6 0	−
h m n	m n	occ. p thog c n man	+	+	+	+	−	−	−	−	?	−
H K	m n	n o-ph rynx occa o lly	±	−	−	+	−				4 6–4 8	−

an open wound such as a recently extracted tooth green streptococci may gain access to the blood stream and produce *bacterial endocarditis* while actinomyces give rise to local infection of the mandible ("*lumpy jaw*") Saliva has only weak bactericidal properties but it acts as a diluent and efficiently washes bacteria back to the oropharynx where they are swallowed and eventually destroyed by the gastric juices Furthermore the mouth has a particularly rich blood supply and it is known that highly vascular tissues are more resistant to infection

When primary or secondary syphilitic lesions are suspected in the mouth darkfield examination may prove confusing since a large number of spirochetes are normally present They may be so similar in appearance to *Treponema pallidum* that the differentiation should be left to an expert syphilologist (Fig 7 p 46)

The Flora of the Nasopharynx —The nasopharynx has a rich and varied flora In addition to the organisms present in the mouth pneumococci beta hemolytic streptococci influenza bacilli meningococci diphtheroids diphtheria bacilli micrococci such as *M pharyngis siccus* or *M catarrhalis* and various gram negative cocci are found The organisms present in greatest numerical frequency are green streptococci diphtheroids and micrococci The nose in general contains fewer organisms than the pharynx and these are most likely to be white staphylococci and diphtheroids The results of throat culture are often confusing since not uncommonly pathogenic organisms such as the pneumococcus streptococcus meningococcus and influenza bacillus are present It is a mistake to assume that such organisms are necessarily or invariably responsible for the patient s illness

As with all laboratory data the physician must use his judgment in their evaluation In the presence of an obvious pharyngitis a throat culture which reveals a preponderance of hemolytic streptococci is almost certain proof of the etiological diagnosis Under the same clinical circumstances the presence of only one or two colonies of hemolytic streptococci leaves the etiology in doubt and requires a repetition of the culture

Green and indifferent streptococci are normal saprophytic inhabitants of the nasopharynx without clinical significance unless they gain access to the blood stream On the other hand hemolytic streptococci are potential pathogens The physician should never accept a report of streptococci present in the throat but should insist upon knowing whether they are *green indifferent* or *beta hemolytic* Even the presence of the latter is by no means always associated with disease From 1 to 10 per cent or more of normal persons may be temporary healthy *carriers* of hemolytic streptococci especially in the winter At times the carrier rate of hemolytic streptococci may exceed 30 per cent The physician should ask for a statement of the quantitative distribution of the flora obtained from a throat culture Obviously one or two colonies of hemolytic streptococci are of less importance than an almost pure culture

Pneumococci are present in the nasopharynx of at least 50 per cent of normal persons at one time or another during the course of the year Most of them are of the higher types and are of low or doubtful virulence A small proportion of persons (1 to 2 per cent) are normal healthy carriers of the Types I II V VII which are responsible for most cases of lobar

present the clot is not dissolved Procedures for the determination of streptolysins S and O have also been developed but they are technically difficult and at present can be carried out successfully only in research laboratories

In addition to the specific antibodies recovery from hemolytic streptococcal infection is associated with the development of *bactericidins* and *opsonins* These are present so inconstantly and to such a variable degree that they do not lend themselves to standardized procedures

Primary Local Streptococcal Infections—Local streptococcal infections are frequently encountered on the surface of the body or in any of the cavities The commoner clinical entities include *abscess cellulitis lymphangitis lymphadenitis oral sepsis tonsillitis* ascending infections of the *urinary tract prostatitis endocervicitis rhinitis sinusitis* and *nasopharyngitis* Each of these conditions is described in the several chapters dealing with local infectious processes The general principles of therapy include topical applications of *penicillin* as in staphylococcal lesions the systemic use of *sulfonamide* for the ambulatory patient and *penicillin* if injection therapy can be maintained

Secondary Streptococcal Infections—Streptococci often produce complicating *or secondary infections through invasion of tissue previously* damaged by other primary invading micro organisms Thus on the surface of the body streptococcal infection may be superimposed on a *dermatophytosis* (p 3293) producing *erysipeloid dermatophytosis* Following an upper respiratory infection of virus origin the streptococcus may invade the inflamed tissues and produce inflammatory complications in the nose throat accessory sinuses middle ear or mastoid process the invasion may involve the lower respiratory passages and an atypical pneumonitis usually of virus origin is complicated by a coccal bronchitis pneumonia or thoracic empyema The meninges become contaminated by way of *the nose or ear* and a rhinogenic or otogenic meningitis is established Streptococcal peritonitis usually occurs by extension and tuberculous tissue often affords favorable conditions for secondary streptococcal growth and invasion

The clinical management of complicating streptococcal lesions presents many difficulties The practitioner must recognize first that he is dealing with a streptococcal infection and second that there is an underlying or coincidental primary affliction Knowledge of the first of these facts stimulates him to inaugurate and persist in specific anti infective therapy recognition of the presence of the prior invasion cautions him to be *guarded* in his prognosis and wary in his interpretation of the significance of beneficial results Exemplifying these general principles anti infective therapy may be beneficial in the management of a persistent or severe virus pneumonitis with a complicating streptococcal invasion The inauguration of sulfonamide or penicillin therapy is dependent upon the hope of conquering the secondary rather than the primary infectious agent The prognosis is guarded since the practitioner recognizes that the virus element may persist after the coccal participation has been terminated if a thoroughly satisfactory outcome is experienced *the happy eventuality is attributed* not to a specific effect on the virus but to conquest of the secondarily invading streptococcus

Streptococcal Toxemia—The effects of streptococcal toxin are most ob

The normal duodenum and upper jejunum contain very few organisms but the lower part of the small intestine and especially the colon contain an enormous bacterial growth Probably a third of the dried weight of the feces is composed of bacterial bodies

The large intestine is a veritable culture tube in which definite bacterial types struggle constantly to gain supremacy (Rettger) In the adult intestine there is a gradual and relative increase in organisms of the coli group which eventually constitute about 75 per cent of the entire flora In addition the following organisms are commonly found enterococci staphylococci both white and yellow aciduric bacilli chiefly *Lactobacilli acidophilus* anaerobic spore bearing bacilli including *Clostridium welchii* proteus organisms Friedlander bacilli *Bacillus subtilis* and *mesentericus* and yeasts of various types A considerable proportion of the bacterial population consists of anaerobic organisms Protozoa such as *Endamoeba coli* are normally present and of no importance except that they may be mistaken for the pathogenic *Endamoeba histolytica* (amebic dysentery)

Pathogenic typhoid Salmonella and dysentery organisms also may be found in the feces in clinical disease or in the carrier state in health Since these organisms are morphologically indistinguishable from harmless coliform bacilli culture methods are required for their identification The protozoal and helminthic infestations of the bowel are recognized by gross and microscopic examination of the stool

Diet and the character of the fecal residue play an important role in determining which of the bacterial types is to gain predominance A high carbohydrate diet favors the development of a gram positive flora The supremacy of certain of the gram positive organisms such as *Lactobacillus acidophilus* may be furthered by feeding lactose or by actually introducing cultures of the bacillus by mouth or by rectum Many clinicians who believe in the importance of intestinal auto intoxication favor the artificial production of a bacterial flora resembling that of infancy

With great excess of carbohydrate in the intestinal tract particularly in the absence of the lactic acid products conditions are favorable for the growth of *B welchii* These organisms produce acids and it is claimed may initiate an enteritis and colitis The antagonism between *B acidophilus* and *B welchii* may be employed in therapy Parenthetically the widely advertised Bulgarian lactobacillus despite enthusiastic claims cannot be implanted in the large bowel

Whether the normal bacteria of the intestine are useful or harmful is a vexed and unsettled problem Favorable reactions of bacteria include the synthesis of vitamin K and the beneficial effects on processes of digestion The noxious influences of intestinal bacteria are less clearly demonstrable From the time of Metchnikoff many clinicians have viewed the intestinal flora with dark suspicion regarding a wide variety of clinical disturbances as manifestations of bacterial activity in the bowel The problem of auto intoxication is clouded by opinions and prejudices and clarified by little experimental evidence one way or the other

The Flora of the Urethra and Vagina *Male Urethra*—The anterior urethra of males contains few organisms and these mainly consist of white staphylococci and diphtheroids Sometimes short gram negative bacilli in

Diagnosis of Streptococcal Disease

Localized streptococcal infection is diagnosed by the recognition of the organism in smears or cultures Infected material should be cultured on pour plates of blood agar to observe the phenomenon of beta hemolysis

Perhaps one of the commonest clinical misconceptions is that which accepts without question an etiologic relationship between a positive smear or culture and the disease under observation Too often any throat infection from which a streptococcus can be cultured is regarded as a streptococcal or septic sore throat and intensive chemotherapy is instituted often unnecessarily and occasionally to the detriment of the patient

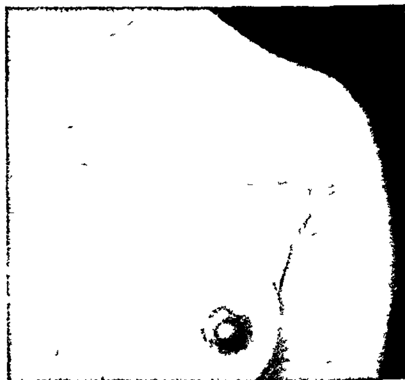


Fig 18 —Schultz Charlton blanching reaction

Blood cultures (q v) in the presence of an invasion with the hemolytic streptococcus present little technical difficulty for the bacteriologist The practitioner must recall however that in subacute bacterial endocarditis there may be considerable difficulty in isolating the alpha and gamma varieties Some of these organisms grow very slowly and the cultures should be incubated for one or two weeks before they are discarded as showing no growth

Skin Reactions (Dick and Schultz Charlton Tests) —Skin reactions are of considerable value in the recognition of susceptibility or immunity to scarlet fever and in the diagnosis of this disease A positive reaction to the intracutaneous injection of erythrogenic toxin (*Dick test*) indicates susceptibility to scarlet fever while a negative reaction is ordinarily indicative of

* From Dick and Dick *Scarlet Fever* Year Book Publishers Inc Chicago Ill

CHAPTER 4

COCCAL INFECTIONS STAPHYLOCOCCUS, STREPTOCOCCUS, PNEUMOCOCCUS

THE STAPHYLOCOCCUS

STAPHYLOCOCCI are commonly present on the skin and mucous surfaces of the upper respiratory tract and genitalia in the air and on food Although the great majority of staphylococci are harmless saprophytes others are pathogenic their invasiveness being determined by the state of the host s resistance and the inherent virulence of the organisms

Bacteriology.—Staphylococci appear in grape like clusters when spread and stained from cultures or pyogenic exudates They are characteristically gram positive although in old cultures degenerative gram negative forms may be encountered Staphylococci are non motile and do not form spores Capsules are generally not d monstrabl Staphylococci are readily grown in plain infusion broth or on the surface of infusion agar plates They grow aerobically at a temperature of 37 C The commonly encountered types of staphylococcus are the *aureus* and the *albus* vari ties Virulent strains generally belong to the former type

Staphylococcus albus produces an opaque white colony on the surface of plain agar *Staphylococcus aureus* a golden yellow pigmented colony which is fairly larg opaque and marked with a defin te edge The aureus pigment may not develop fully in twenty four hours incubation and it sometimes requires an additional period of standing at room temperature before it reaches maximum development

Staphylococci are fairly heat resistant and may survive exposure to 63 C for thirty minutes They are easily killed however by many of the anil n dyes such as gentian violet (1 125 000) or by cresol (1 90)

Toxin Production.—Staphylococci elaborate a number of soluble toxic products of importance in the pathogenesis of infection These tox ns which may be separated by Berkefeld filtration include leukocid n hemolysin necrotizing lethal and enterotoxic factors coagulase and a spreading factor

The add tion of *leukocid n* to a suspension of polymorphonuclear leukocytes inhibits phagocytosis and often results in the death of the white cells The *hemolytic factor* occu s in two arieties the *alpha* which lyses sheep and rabb t red blood corpuscles when incubated at 37 C and the *beta* which is inert for rabb t red cells but lyses human erythrocytes and also sheep cells if the latter are chilled after a preliminary period of incubation at 37 C The *dermatonecrot c factor* produces a sloughing lesion at the site of the inoculation when injected locally into the skin of a rabbit The *lethal* staphylococcic toxin in ected intravenously into rabbits causes the death of the animal in five to ten minutes The *hemolytic dermatonecrotic* and *lethal* factors are usually viewed as d fferent manifestations of a single substance acting under varying ci cumstances

Enterotoxin is distinct from the other substances and is usually obtained by growing staphylococci in semi-sol d agar under increased carbon d oxide tension This toxin is not heat susc ptible and even resists boiling for a few minutes When enterotoxin is fed to monkeys or injected intraperitoneally or intravenously into young k ttens it produces nausea and violent diarrhea Man is apparently far more susceptible to this toxin than the laboratory animal Many instances of human food poisoning are caused by staphylococcus enterotoxin

In addition to these toxins the staphylococci elaborate a *coagulase* and a *spread g factor* By virtue of the former many pathogenic strains have the property of coagulating plasma a fact wh ch may explain the ten lency for the localization of staphylococcal infections As opposed to this the spreading factor causes increased disseminat on of material that has been injected into the skin

strengthening of the mechanisms of defense by such procedures as repeated transfusions of whole blood Surgery is required for the drainage of pockets of pus and for the ligation or excision of segments of veins involved in the bacterial invasion

Topical and systemic anti infective therapy present the same great promise and the same choices as in staphylococcal afflictions For topical use the practitioner may choose 1 per cent gentian violet 5 per cent sulfathiazole 0 04 per cent tyrothricin or a solution of penicillin (250 to 10 000 units per cubic centimeter) Again our preference is for penicillin on the grounds of lesser toxicity greater bactericidal potentiality and absence of the phenomenon of sensitization

For systemic anti infective therapy the practitioner may use either a sulfonamide or penicillin Our sulfonamide preference is for *sulfadiazine* with sulfamerazine for second choice and sulfanilamide as a third choice The sulfonamides may be given orally for the ambulatory patient but the seriously ill merit the intravenous injection of a sodium salt in 5 gm dosage *With at least equal potency and lesser risk penicillin may be ad*ministered intramuscularly or intravenously and when the situation is critical the combination of penicillin and sulfonamide may be employed with benefit In overwhelming protracted or seemingly resistant infection especially in the weakened the aged and the very young high concentrations of penicillin effected by massive dosages of 500 000 to 4 000 000 unit daily are worthy of earnest consideration Resistant organisms finally may prove streptomycin sensitive (p 103)

Serums and Vaccines—Because of the great potency of the anti infective agents streptococcal serums and vaccines occupy the position of desperation remedies in the few clinical situations in which the more powerful agencies fail to produce their customary beneficial effects The officinal serums include *Erysipelas Streptococcus Antitoxin N N R Scarlet Fever Streptococcus Antitoxin N N R Anti erysipelas Anti bacterial Serum N N R* and *Human Scarlet Fever Immune Serum* obtained from convalescents

A consideration of the diversity of streptococcal types and subtypes as elucidated in the preliminary section on Bacteriology emphasizes the slim chance of accomplishing great benefit from the use of the specific serums Injection methods are cumbersome and the risk of serum reactions constitutes *a genuine hazard*

Vaccine therapy in streptococcal infection is of very questionable value Certainly the polyvalent stock vaccines hold little promise of significant beneficial reaction against a specific streptococcal strain In rare instances an autogenous vaccine may be utilized in recurrent or persistent inflammation

Preventive Treatment—The prevention of hemolytic streptococcal infections is a major problem in public health It has not yet been met or even faced in the light of present day knowledge of the epidemiology of the hemolytic streptococcus Scarlet fever septic sore throat erysipelas and puerperal sepsis are *reportable diseases* in most communities Isolation of the patient to prevent further dissemination of the organism and quarantine of contacts particularly those who are susceptible is generally enforced

Local Lesions—The staphylococcic dermatoses (p 3248) include furuncle carbuncle pustular folliculitis sycosis vulgaris impetigo contagiosa furfuraceous impetigo bullous impetigo dermatitis exfoliativa neonatorum ecthyma axillary sweat gland abscess paronychia granuloma pyogenicum infectious eczematoid dermatitis and dermatitis papillaris capillitii

Secondary Infections—Secondary staphylococcic infections occasionally occur by continuity but they may also follow primary invasions produced by other organisms

By direct extension from the nose or ear staphylococci may invade the meninges and give rise to *rhinogenic* (p 2128) or *otogenic meningitis* (p 2148)

Staphylococcal infections also involve the upper respiratory tract where they produce secondary invasion following virus diseases such as the common cold and influenza Under these circumstances with the lowered tissue resistance the staphylococcus invades the nasal passages producing *subacute chronic* or *recurrent sinusitis* or sets up an *otitis media* or *mastoiditis* (p 2146)

Food Poisoning—The enterotoxin of the staphylococcus produces food poisoning to which reference is made more fully in the chapter dealing with Disturbances of Digestion (p 1809) Epidemics resulting from ingestion of custard filling sauces milk or cheese are usually staphylococcal since the food is a fine culture medium for the organism The origin of the disturbance is usually a finger infection of a food handler

See *Differential Diagnosis of Food Poisonings* (p 240)

Staphylococcemia—A bacteremia with the staphylococcus is almost invariably a secondary manifestation It usually results when a virulent organism enters the blood stream most often as the result of the penetration of an abscess directly into the wall of a vein In this respect *furuncles about the nose and upper lip* hold the greatest threat The angular vein which leads into the cavernous sinus becomes involved with a resultant staphylococcemia

The *clinical manifestations* of the ominous complication consist of increasing toxemia the presence of a febrile reaction often with chills The patient seems ill out of all proportion to the extent and intensity of the local process In debilitated patients and in the newborn the bacteremia more often results from the weakened defenses of the host than the virulence of the organism Under those circumstances there is no marked immunity reaction and the finding of the positive blood culture is often in the nature of an unexpected discovery

Metastatic Infections—Staphylococcemias occasionally produce metastatic furuncles *Pulmonary furunculosis* (p 2212) is a highly fatal complication since the local lesions are not accessible to surgical interference The renal complication often takes the form of a *renal carbuncle* or a *perinephric abscess* Localization in bone may result in *osteomyelitis* or a *bone abscess* (p 2030)

Diagnosis

The diagnosis of staphylococcal infection is usually suggested by the appearance of the local suppurative process The invading organism is

patient himself is the carrier and that he reinfects himself by transferring organisms from his nasopharynx to minor breaks in the skin

The *communicability* of erysipelas is no greater or less than the communicability of streptococcal disease in general Strict precautions should be taken to prevent the patient from infecting his medical attendants and also to prevent the transfer of the infection from one site to another

Pathogenesis and Immunity —The local erythema and the systemic toxemia of erysipelas are somewhat analogous to the manifestations of scarlet fever and suggest that erythrogenic toxin may play a significant role in its pathogenesis Despite this antitoxic immunity sufficient to protect against the development of a scarlatinal rash confers no protection against erysipelas and Dick negative individuals are susceptible to the disease Not only does erysipelas fail to confer any degree of lasting immunity but one attack frequently predisposes to another

Pathology and Bacteriology —The lesion of erysipelas is confined principally to the epidermis and superficial layers of the skin Mononuclear cells are found in large numbers in the corium The organisms are present in the lymphatics of the involved area and are most readily demonstrable at the margins of the lesion They are rarely present in the blebs or vesicles which form on the surface A positive culture is obtained most readily by injecting a small amount of saline solution intradermally in the margin of the lesion and raising a bleb from whose contents streptococci usually can be recovered Ordinarily hemolytic *streptococci of the same type can be recovered from the nose and throat. When patients are severely ill the blood stream is invaded and the organism can be obtained by blood culture*

Clinical Features —The *incubation period* of erysipelas is short and probably does not exceed four days The *onset* is abrupt with such constitutional manifestations as fever, chilliness (or often a frank chill) nausea vomiting and soreness of the throat

The Local Lesion —In the vast majority of instances the lesion of erysipelas occurs on the face most commonly on the *cheeks* and *nose* (Fig 19) Most often the eruption is unilateral although it may spread across the nose in a somewhat *suggestive 'butterfly pattern* Only occasionally does erysipelas involve the extremities or trunk Multiple areas of involvement are uncommonly observed

Attention is soon drawn to the area of local involvement by a *burning sensation* accompanied by redness and swelling The lesion soon becomes painful and tender to pressure progressing to an angry redness which by older clinicians was termed *St Anthony s fire* The local lesion is circumscribed slightly elevated red hot and tender *Vesicles* and *bullae* appear on the surface and in the severer instances there may be hemorrhage into the skin

The *progression* of the lesion is as characteristic as its appearance The process spreads rapidly Its margins are elevated and there is a sharp line of demarcation between normal and involved tissue This characteristic feature is noticeable especially on the face where the skin is tightly bound down to the deeper tissues In areas where the skin is looser the margins of the lesion are less distinct and the pain and tenderness are correspondingly less

In summary then a patient with facial erysipelas presents an unmistakable appearance *The lesion usually involves the cheeks* and the nose and may often assume a butterfly distribution by progression over the bridge of the nose The eyelids are greatly swollen often to the extent of partial or complete closure of the eyes Although the greater part of the face may be involved the infection usually is sharply limited at the hair line above and the jaw below

500 units Under these circumstances if 2000 cc are given daily the patient receives a twenty four-hour dose of 500 000 to 1 000 000 units which should be *quite sufficient to control any bacteremia that is amenable to anti* infective therapy A second exception to intramuscular injection exists in meningitis which is usually rhinogenic or otogenic An insufficient concentration of penicillin is maintained in the cerebrospinal fluid unless the agent is given intrathecally To accomplish effectual control a lumbar puncture is performed and the drained spinal fluid is replaced by a solution containing 10 000 to 20 000 units of penicillin Little of this passes the cerebrospinal barrier and enters the systemic circulation so that an effectual local concentration is maintained for a long period of time and a repetition of the dose may not be required for eight to twenty four hours Penicillin like other foreign bodies produces a pleocytosis in the cerebrospinal fluid so that the progress of the lesions is best judged by the clinical phenomena and the morphologic and cultural characteristics of the withdrawn fluid

Systemic anti infective therapy of staphylococcal infections may also be carried out with sulfonamide Again our preference is for sulfadiazine which may be administered orally in the manner described above for the severely *infected* ambulatory patient Should the situation be more critical a large initial dose may be given intravenously using the sodium salt in 5 or 25 per cent solution If the weaker solution is used at least 100 cc are injected to give a priming dose of 5 gm (75 grains) If the stronger solution is available an exceedingly slow intravenous introduction may be attempted by means of a 20 cc syringe Under the latter circumstance an entire barrelful delivers the 5 gm initial amount

Our choice of penicillin rather than sulfonamide is based entirely upon the fear of toxicologic manifestations in the use of the latter Many of these sequels are unpredictable and due to idiosyncrasy some have *only* nuisance value as exemplified by the drug fevers and the toxicodermas but others are of considerable magnitude particularly those that involve the blood and blood forming organs the liver and the kidneys The innocuousness of penicillin is in sharp contrast to the occasional treachery of the sulfonamides from our personal standpoint there can be little argument concerning the greater desirability of making a first effort with the penicillin

It is our opinion that the introduction of the sulfonamides may be postponed until the effects of penicillin therapy have been observed After twenty four hours if the patient is not significantly improved and there is no surgical indication for drainage or eradication of a focus the penicillin may be fortified by the simultaneous administration of a sulfonamide preferably sulfadiazine in the manner above indicated Again it is emphasized that sulfathiazole has a poor penetrating power for the cerebrospinal fluid and should not be used in the event that the clinical condition *is of* meningitic character It is worth emphasizing again that anti infective therapy is no substitute for indicated surgery nor can it be *successful if* the resistance of the host is not fortified by the measures next described

Many *staphylococci* are quite resistant to sulfonamide and require high concentrations for long periods of time others tend to become drug fast requiring a change of preparation or a switch to penicillin if sulfonamide alone has been employed

DIFFERENTIAL DIAGNOSIS OF

Generalized Rashes in Eruptive Fevers

Before entering into a discussion of scarlet fever the first of the exanthems to be treated in this section it seems fitting to deal with the broader problem of the differential diagnosis of generalized rashes in the febrile and afebrile

The day has long since passed when the practitioner can regard the acute exanthems as con isting of measles scarlet fever rubella and chickenpox He has since learned that a generalized eruption may be an integral part of meningococcemia infectious mononucleosis spirochetal invasions (especially syphilis) or rickettsial disease (such as typhus and spotted fever) Difficulties in diagnosis are further increased by the fact that fever and a rash may result from the administration of drugs taken by self medication or prescription in an otherwise non eruptive infection such as the common cold or influenza

Conscious of the many facets to the problem the clinician therefore approaches the diagnosis of the febrile rash with caution and humility avoiding such obvious booby traps as the false positive Wassermann reaction in infectious mononucleosis and the morbilliform or scarlatiniform outbreaks caused by analgesic antipyretics sedatives sulfonamides and arsenicals He realizes that even the expert cannot differentiate eruptions by morphology alone and he does not refrain from collecting all available data before he commits himself to a definite opinion and therapeutic program

Disturbance	Type of Lesion[1]	Herald Site	Spread	Duration from Evolution to Involution	Specific Features
Scarlet Fever	Punctate lesion with confluence to diffuse eryth ema	Neck, chest and skin folds	Arms and legs Cir cumoral pallor	2 to 6 days	Schultz Charlton reaction (Fig 18 p 164)
Meningo-coccemia	Maculopapular petechial or purpuric (Fig 23 p 212)	Body	Shoulders and thighs	2 to 5 days	Headache and meningeal symptoms
Tularemia	Maculopapular and pustular	Body	Irregular	Irregular	Handling ro-dents Tick bite
Syphilis	Maculopapular erythema vesicular or pustular (Fig 49 p 338)	Irregular	Irregular	Irregular	History of chan cre (p 335) Positive dark field and serol ogy (p 337)
Rat Bite Fever	Maculopapular	Chest and arms	Irregular	Irregular	History
Typhus Fever	Maculer and petechial (Fig 57 p 370)	Axilla and loins	Abdomen chest and back	2 to 10 days	Epidemic Weil Felix reaction (p 372)
Rocky Moun tain Spotted Fever	Maculopapular and petechial (Fig 58 p 378)	Wrists ankles	Scalp chest abdomen	2 to 3 weeks	Tick bite

The single exception to the policy of conservatism in staphylococcic infection exists when there are evidences of staphylococcemia such as a positive blood culture or the presence of chills with a swinging septic temperature Under these conditions it may be hypothesized that a vein wall infection has occurred and *immediate wide excision* of the segment is indicated *Preceding and following all surgical procedures the patient should have the advantage of prophylactic penicillin and sulfonamide therapy*

SPECIFIC IMMUNOTHERAPY

Specific systemic therapy by biological means is attempted with the official *Staphylococcus Antitoxin N.N.R* whose efficacy is questionable and usefulness controversial to say the best The serum is prepared through the immunization of horses and the dangers of injection seem to outweigh by a considerable margin any anticipated beneficial results The indication for its use is a desperation effort when chemotherapy has failed to halt a generalized overwhelming infection

PROPHYLACTIC IMMUNIZATION

Staphylococcic vaccines toxoids and the bacteriophage have been employed but specific prophylactic immunization by biological products for the most part is quite disappointing and perhaps valueless The staphylococcus vaccine may be of polyvalent stock variety or it is prepared autogenously In our experience only the latter has possible value but even this is open to question Injections must be given over a long period of time beneficial results are not invariably encountered and those that are seen may as well have resulted from local and systemic non specific measures

Staphylococcic Toxoid N.N.R is available It may be employed as a second best method of producing an active acquired immunity when autogenous vaccines cannot be obtained The use of *specific bacteriophage* cannot be considered by the general practitioner The material is too difficult to obtain and the results even in the most expert hands are far from convincing and indeed may be labelled as disappointing

THE STREPTOCOCCUS

Streptococci are a large group of morphologically similar organisms widely distributed in nature The present concern is the relatively small group which are actual or potential agents of human disease

Bacteriology —Streptococci are commonly present in the upper respiratory tract, on the oral mucosa and on the skin in the lower intestinal canal and in vaginal secretions In most instances surface organisms are nonpathogenic but they may also be isolated from inflamed tissues under circumstances which leave little doubt as to their etiologic role in disease

Morphology and Cultural Characteristics —The individual streptococcus is a spherical organism from 0.5 to 1.0 micron in diameter It occurs in chains of from two to more than a dozen organisms The virulent Group A beta hemolytic strains form capsules in the early stage of their growth Streptococci are non motile and do not form spores They are gram-positive although in old laboratory cultures they may turn gram negative

Streptococci are easily cultured on enriched laboratory media The medium of choice is meat infusion broth or agar to which 5 to 10 per cent of horse sheep or rabbit blood is added Most strains are aerobic but some are anaerobic or micro aerophilic Organisms of the latter type often produce chronic progressive ulceration of the skin and cultures taken from such lesions should therefore be incubated anaerobically

DIFFERENTIAL DIAGNOSIS OF

Generalized Eruptive Fevers by Features Other Than the Rash

Only the bold and experienced expert a sumes that it is possible to make the diagnos s of an eruptive fever by observation of the morphology of a rash For the vast body of clinicians it is neces ary to weigh accompanying subjective objective epidemiologic and labor tory data before an expression of opinion is justified

Disturbances	Constitutional Symptoms	Suggestive Objective Findings	Laboratory Data	Specific Tests
Scarlet Fev r	Mild to severe	Pharyngotonsillitis Strawberry tongue (Fig 20 p 177)	Leukocytosis Eosinophilia	Schultz Charlton reaction (Fig 18 p 164)
Meningococcemia	Mild to fulminating	Headache Stiff neck	Bacteremia Turbid spinal fluid with gram negative cocci (Fig 8 p 47)	Stain gram negative coccus from blood of skin lesion
Tularemia	Mild to severe	Primary papule at site of bite	Leukocytosis Agglutinins (p 59)	Bacteremia Skin test (Fig 325)
Syphilis	Absent to mild	Healed chancre	Positive darkfield (p 336)	Positive serology (p 337)
Pat Bite Fever	Mild to moderate	Bite with lymphangitis	Leukocytosis False positive Wassermann	Spirochetes on aspiration of node
Typhus Fever	Moderate to severe	None	Leukocytosis	Weil Felix reaction (p 372)
Rocky Mountain Spotted Fever	Moderate to severe	None	Leukocytosis	Weil Felix reaction (p 372)
Dengue	Moderate to se e e but brief	None	Leukopenia	None
Measles	Moderate to severe	Catarrhal respiratory symptoms	False positive Wassermann (p 337)	None
Pubella	Mild	Posterior cervical lymphadenopathy	None	None
Fourth Disease	Mild	None	None	None
Fifth Disease	Mild	None	None	None
S xth Disease	Moderate	None	Leukopenia	None
Chickenpox	Mild	None	None	None
Smallpox	Moderate to severe	None	None	None

tain The test is performed by extracting C substance from the bacteria and layering it over anti C serum obtained by immunizing rabbits When the test is positive a white *ring forms* at the interface between the streptococcus extract and the grouping serum

The Strains of Beta Hemolytic Streptococci—Through the precipitin test groups of beta hemolytic streptococci are *recognizable Group A is the most important since it includes* almost all of the strains pathogenic for man (scarlet fever septic sore throat erysipelas and puerperal sepsis) *Group B strains* account for most instances of *bovine mastitis* This variety is also commonly found in the human nasopharynx but rarely gi es rise to clinical disease *Group C strains* of beta-hemolytic streptococci account for numerous animal infections but only occasionally may be pathogenic for man *Group D strains* are rarely pathogenic They were originally isolated from cheese and include the enterococci commonly present in the *human intestinal tract Group E strains are normally found in raw* milk but are not responsible for human d sease and specifically are not the cause of epidem cs of milk borne septic sore throat or scarlet fever *G oups F G H and K* are nonpathogenic streptococci found in the human nasopharynx and *groups L* and *M* have been isolated in dogs In the appended table adapted from Lancefield the serological groups are correlated w th their hemolytic activity and with certain metabolic characteristics

Types of G oup A Beta-Hemolytic Streptococci—The Group A beta hemolytic streptococci have been subdivided *into about* thirty types on the basis of two other antigenic fractions a nucleoprotein M substance and a 'T *substance* Typing of Group A hemolytic *streptococci is of great* epidemiological importance *although the method at present is* too complicated and uncertain for general laboratory use

See *Differential Diagnosis of Commoner Febrile Skeletal D sorders* (p 192)

The Specificity of Streptococci—The typing of hemolytic streptococci has altered profoundly older concepts of the specificity *of* streptococcal strains It was formerly thought that scarlet fever was produced by one strain of hemolytic streptococci erysipelas by an other and septic *sore* throat by still another Specific names were given to *these strains* such as *Str scarlatinae Str epidemicus etc It is now clear* that any one of the *th rty odd* types of Group A may give rise to any one of the many manifestations of hemolytic *streptococcal infection There is no clear* evidence that any one type is *likely to produce but one* clinical type of disease In a given year some types are more prevalent than others and moreover a given type may appear more virulent and invasive in one year than in another

Typing of Streptococci in Relation to Ep demiology—The typing of Group A hemolytic streptococci has been of great value *in* tracing the transmission of the organism from case to carrier to contact and has contributed greatly to the understanding of cross infection especially as observed in hosp tal wards For example it has been found that wh le *streptococci are not uncommon in the genital tract during* labor Group A strains are but rarely found there The majority of hemolytic streptococcal *puerperal infect ons* are due to *strains transm tted from the nasopharynx* of the patient herself *or* from the *respiratory* mucosa of the attendants The late septic *compl cat ons of sca let fever* are frequently due to Group A streptococci of other types acquired from contact with the pat ent s atte dants or others in a ward rather than to the strain wh ch initiated the patient s own disease Similar observat ons have been made in regard *to postoperative wound infect ons* These findings emphasize the importance of preventing transmission *of* hemolytic streptococci It *is* hoped that ultraviolet irrad ation and chemical sprays will prove more valuable than the tr d tional but inadequate gown *and mask technic in* the preventing of spread *of hemolytic* streptococci

Toxin Production—The pathogenesis of beta hemolytic streptococcal *infections (Group A)* has been clarified to a certain *extent* by the study of the extracellular substances which these o ganisms elaborate One such substance *fibrinolysin has* the ability to d ssolve fibrin clots Another *streptolysin* is the factor respons ble for the hemolysis of red *blood cells* Streptolysin occurs as streptolysin O which is reversibly inactivated by oxygen but not by acid and streptolysin S which is destroyed by heat and ac d but not by oxidation

Streptococci also produce *leukocidin* which has the ability to destroy *leukocytes* Another substance as yet *incompletely ident fied* but possibly related to *hyaluronidase* enhances the abil ty of streptococci to spread through tissues This *spread ng factor* has also been ident fied in *other micro-organisms including the Welch bacillus and staphylococcus* Finally *hemolytic* streptococci elaborate a soluble heat resistant *exotoxin* the *erythrotoxin* wh ch *is responsible for* the eruption *of scarlet fever* and probably for some of th other toxic manifestations of this and other streptococcal infections

constant There is no satisfactory explanation for these periodic alterations in severity Thirty or forty years ago scarlet fever was a serious disease with a high mortality rate today however it is remarkably mild with an overall mortality rate of not more than 1 per cent. The severe toxic and septic types of the disease whose case mortality rates rise at times to 25 per cent are but rarely seen This fact has deterred health authorities from instituting vigorous campaigns for active immunization although there is no assurance that the disease may not again become prevalent in severe form

Scarlet fever is most frequently observed in the *winter* and *early spring* when all types of hemolytic streptococcal infections are most prevalent It is worldwide in distribution and is common in temperate climates but rare in the tropics

In the great majority of instances the spread of organisms occurs by *direct contact* or *droplet transmission* from the pharyngeal mucosa of the patient Indirect transmission by fomites and especially by dried secretions is probably common *Healthy carriers* of hemolytic streptococci are undoubtedly of great importance in spreading the disease So-called *surgical scarlet* results from the infection of wounds and puerperal sepsis from contamination of the uterus by hemolytic streptococci

In general the *communicability* of scarlet fever is not to be compared with that of measles or whooping cough and is probably of about the same order as diphtheria The secondary attack rate calculated by the proportion of susceptible contacts who contract the disease following exposure to a known case is less than 15 per cent and in a recent study it was only 4 per cent These figures apply only to those patients who develop a rash, since that is the only epidemiological criterion by which the disease can be recognized A great many more contacts become carriers of hemolytic streptococci These may develop pharyngitis and septic complications but because they have circulating antibodies to the erythrogenic toxin they do not develop recognizable scarlet fever

From this point of view a patient with scarlet fever is neither more nor less infectious than any other individual harboring large numbers of hemolytic streptococci and hence it is obvious that present day quarantine and isolation regulations for scarlet fever are antiquated It seems inconsistent that patients with a rash are segregated in a special fever hospital or isolated at home while streptococcal pharyngitis without a rash is not a reportable disease and is cared for without precautions at home or on the wards of general hospitals

Immunity—The varying invasive reactions of a single strain of hemolytic streptococcus are due in part to differences in the infecting dose but chiefly they are the result of different degrees of immunity to the erythrogenic toxin Surveys made by means of the Dick test indicate that susceptibility or immunity to erythrogenic toxin varies widely according to age. More than half of infants under six months of age have an immunity that is probably the result of passive transfer of antibodies from the mother In children from one to three years of age immunity (Dick negativity) is present in only 30 per cent but thereafter immunity rises steadily with advancing age so that 80 per cent or more of adults in urban communities are Dick negative Corresponding with these figures the prevalence of clinical scarlet fever is greatest in childhood Fifty per cent of the patients are in the age group of one to five and 80 per cent are under ten years of age.

As determined by Dick testing and clinical experience an attack of scarlet fever results in durable if not permanent immunity yet this immunity is directed only against the erythrogenic toxin An individual who has recovered from scarlet fever is quite as susceptible to further infection with hemolytic streptococci as one who has never had the disease Since only about 15 per cent of adults give a history of having had recognized scarlet fever while some 75 to 80 per cent of adults are Dick negative (immune) it is probable that the great majority of adults in urban communities develop active immunity to the erythrogenic toxins by repeated subclinical contact with hemolytic streptococci The high incidence of healthy carriers of hemolytic streptococci many strains of which form erythrogenic toxin supports this hypothesis These immunological data have more than academic significance, since they indicate that many so-called idiopathic or inexplicable sequels such as glomerulonephritis that are commonly attributable to scarlet fever may as well follow other less dramatic instances of invasion with hemolytic streptococci

Pathology—The pathology of scarlet fever is not specific The rash caused by erythrogenic toxin produces mild inflammatory skin changes Fatal cases show pathological changes resulting from toxemia or sepsis In the toxic form of the disease death results generally from *acute myocarditis* with cloudy swelling and degeneration of muscle fibers In septic cases there is bacterial invasion of various organs with abscess formation

Recognition of the action of these extracellular substances explains some of the path ological characteristics of hemolytic streptococcal infection For example streptococcal infections have a tendency to spread through the tissues rapidly producing thin serous pus in contradistinction to the staphylococcus which tends to form local abscesses with thick pus The actions of fibrinolysin leukocidin and the "spreading factor probably account for these effects, since they have the property of breaking down the leukocytic and fibrin barriers of the host's defense reaction thereby permitting the infection to spread rapidly through the tissues and invade the lymphatics and blood stream Erythrogenic toxin accounts for the cutaneous manifestations of hemolytic streptococcal infections and the streptolysins may produce in part the severe anemia that occurs in prolonged infections

Epidemiology—Hemolytic streptococci can be cultured with considerable frequency from the nasopharynx of normal persons Different surveys have yielded quite divergent results the figures varying from 1 per cent to as high as 80 per cent, with an average figure of about 10 per cent From 60 to 90 per cent of these hemolytic streptococci are members of Group A and are potentially pathogenic The prevalence of normal carriers of hemolytic streptococci is probably higher in children than in adults The organisms are most frequent in temperate climates but are by no means rare even in the tropics

Carrier rates rise highest in the winter and early spring coincident with the greatest prevalence of hemolytic streptococcal infections Both patients and carriers are responsible for the dissemination of the organisms but the carrier is undoubtedly of greater importance. The majority of carriers are healthy and do not suffer from recognizable disease The carrier however may at any time develop clinical infection Following upper respiratory streptococcal infection the organisms continue to be harbored in the nasopharynx for periods varying from days to several months Occasionally they can be found in the paranasal sinuses and in the posterior nasal tissue without being detected by throat cultures

Direct person to person transmission by coughing and sneezing was formerly regarded as the chief method of dissemination of streptococci and without doubt it is an important factor in the spread of the organisms In recent years however there has been renewed interest in the theory of *air-borne transmission* of respiratory diseases According to the proponents of this theory the greatest spread of respiratory infection is produced by small dried droplets floating in air for long periods of time and great distances or by the resuspension of such droplets in air after they have settled to surfaces such as floors bedding and clothes A great deal of experimental evidence has been brought forth in support of this viewpoint and control measures have been inaugurated in institutions and hospitals to prevent the dissemination of respiratory infection by this means The use of ultraviolet irradiation in operating rooms and hospital wards is proving most effective in reducing the possibility of the transmission of hemolytic streptococci from cases and carriers to contacts It is probable that aerosol" sprays may soon come into general use for this purpose

Hemolytic streptococci may contaminate *milk supplies* and result in explosive outbreaks of septic sore throat or scarlet fever While cows are frequently infected with Group B streptococci, clinical epidemics are caused by Group A (human) strains Their source may be milkers who infect the cow's udder or milk handlers who contaminate the milk subsequently Since proper pasteurization destroys hemolytic streptococci such outbreaks occur only among those who drink raw or imperfectly pasteurized milk

Immunity—In general recovery from hemolytic streptococcal infection is not associated with durable immunity Repeated attacks of pharyngitis or tonsillitis are of common occurrence One attack of erysipelas predisposes to others in the same skin site so that even local tissue immunity is not produced *The one exception to the lack of persistence of immunity* in streptococcal disease occurs in scarlet fever Antitoxin produced against the erythrogenic toxin persists in the blood and tissues indefinitely so that second attacks of typical scarlet fever are *extremely rare*

Antibody Responses—Fibrinolysin streptolysin and erythrogenic toxin are antigenic and evoke specific antibody responses by the tissues of the infected host Tests for the detection of these antibodies are now available Of these the best known and most widely used is the *Dick test* by which the presence or absence of specific antibodies for erythrogenic toxin can be determined This is of particular clinical importance in connection with scarlet fever

A simple test has been devised for the detection of antibodies against the fibrinolytic substance elaborated by streptococci This test is performed by incubating streptococci with citrated human plasma If specific antibodies (antifibrinolysins) are not present the fibrinolysin elaborated by the growing organisms will dissolve the clot but if antifibrinolysins are

The Tongue—During the first few days of the disease the tongue is heavily coated At about the time the rash reaches its height the tongue begins to peel first at the tip and margins progressing backward until by the end of the week it is denuded and beefy red with numerous large papillae on its surface This is the *strawberry tongue* (Fig 90) whose recognition is of considerable diagnostic help

Clinical Variations—Clinically scarlet fever may be divided into mild or moderate moderately severe toxic and septic types

In *mild or moderate scarlet fever* the prodromal symptoms are mild the temperature does not exceed 101° F and the rash is light or moderate There are few constitutional symptoms and evidences of toxemia are minimal A great many cases of this type are misdiagnosed The patient is usually convalescent five or six days after the onset Septic complications are infrequent but acute glomerulonephritis may occur two or three weeks later

Moderately severe scarlet fever is characterized by more abrupt onset higher temperature a heavier rash and more evidence of toxemia Complications are encountered more frequently than in the milder type of the disease

Toxic scarlet fever is a severe and often fulminating type of infection The symptoms are due to large amounts of toxin formed by the streptococci which remain localized in the pharynx The rash is heavy and may be hemorrhagic in character Profuse vomiting intense headache epistaxis meningismus delirium and coma may develop soon after the onset The temperature may rise as high as 107° F and death occurs from *toxic myocarditis*

In *septic scarlet fever* symptoms result from direct local extension from the pharynx to surrounding tissues Involvement of the paranasal sinuses and suppurative cervical adenitis are common The streptococci may invade the blood stream producing *metastatic abscesses* in distant organs

Laboratory Data—A *leukocytosis* of from 10 to 20 000 cells per cu mm with a predominance of polymorphonuclear leukocytes is generally encountered There is a tendency toward *eosinophilia* especially after the fifth or sixth day of the disease and at this stage 10 or even 20 per cent of the leukocytes may be eosinophils

Course—In uncomplicated cases the temperature is usually highest at the onset of the infection and begins to decline when the rash develops In a case of average severity the temperature rises to 102° F remains elevated for several days and then gradually declines by lysis reaching normal four to six days after the appearance of the rash

Desquamation is one of the characteristic signs of scarlet fever When the rash has been transitory or of doubtful character the development of typical desquamation may allow the diagnosis to be made in retrospect The completion of desquamation usually takes two to three weeks on the body and even longer on the palms and soles It may begin as early as the fifth day of the disease or as late as the third week In contrast to the branny desquamation of measles in scarlet fever the skin peels in rather large flakes

Complications—Complications are more frequent in untreated scarlet

vious in *scarlet fever septic sore throat* and *erysipelas* The most important and easily recognized of the toxins is the erythrogenic substance which forms the basis for the Dick test and the Schultz Charlton blanching reaction (p 164) The practitioner will recall that any strain of streptococcus may generate erythrogenic toxin and that protection against the substance does not necessarily indicate protection against all streptococci and their products

The treatment of the streptococcal toxemias is best conducted through administration of the *streptococcus antitoxin* (p 84) Chemotherapy does not produce a significant effect on the toxic symptoms though there is no reason for withholding sulfonamides or penicillin when serum is being administered

Streptococcemia —The acute streptococcemias are almost invariably due to invasion with the Group A beta hemolytic streptococci whereas the chronic bacteremias such as occur in subacute bacterial endocarditis are more apt to be produced by the alpha (viridans) or the gamma varieties

Acute streptococcemia most often arises as a result of invasion of the blood stream secondary to a local infection in the skin throat or uterus and in frank venous involvement such as sinus thrombosis The onset of the bacteremia is suspected upon the increase in constitutional manifestations a sharp elevation of temperature and particularly the presence of chills The diagnosis is highly suggestive without laboratory data but is made definitively by the result of blood culture

A *cryptogenic streptococcemia* occasionally results from a seemingly minor local infection or from a puncture wound that has completely healed Under these circumstances the patient has evidence of a severe systemic invasion and the accurate diagnosis is made only when the blood culture is reported The management of this type of bacteremia does not differ from those conditions in which the portal of entry is more obvious The prognosis is more ominous because of lack of evidence of adequate local defense

Subacute and Chronic Streptococcemia —Subacute and chronic streptococcemias are almost always due to the presence of alpha or gamma streptococci These feebly invasive organisms rarely survive in the circulating blood unless they localize on heart valves previously damaged as the result of rheumatic fever congenital abnormality or syphilis Under these circumstances they set up *subacute bacterial endocarditis* (p 1071) whose clinical manifestations are often insidious for long periods of time

Metastatic Streptococcal Lesions —Streptococcal bacteremias may produce metastatic lesions throughout the body The more important clinical manifestations are *iritis* (p 1633) *infectious arthritis* and *osteomyelitis* (p 2936)

See *Differential Diagnosis of Commoner Febrile Skeletal Disorders* (p 192)

Streptococcal Allergy —In addition to its infectious manifestations it appears likely that some of the clinical disturbances associated with streptococcal invasion may be allergic This mechanism is a possible explanation of *chronic glomerulonephritis* (p 2379) and of some of the lesions associated with rheumatic fever (p 180)

antitoxin or convalescent serum in an area of the skin where the rash is heaviest One tenth cc of scarlet fever antitoxin or 0 2 to 0 5 cc of con

DIFFERENTIAL DIAGNOSIS OF

The Commoner Generalized Erythematous or Scarlatiniform Rashes

Generalized erythematous eruptions are most often of infectious origin with the notable exception of dermatitis medicamentosa In childhood the practitioner is mainly concerned with differentiating scarlet fever rubella and infectious mononucleosis In the adult the diagnostic dilemma becomes more difficult since secondary syphilis and drug rashes require additional consideration A history of previous scarlet fever or rubella narrows the possibilities since second attacks of either of these infections are rarely if ever observed. Laboratory findings may add confusion since infectious mononucleosis is frequently accompanied by a false positive Wassermann reaction Unless the patient gives a clear-cut history of exposure to syphilis or presents other manifestations of venereal infection a definite opinion should be deferred and treatment may be withheld until the course of the Wassermann test can be followed during the fading of the heterophile reaction and the disappearance of mononuclear cells from the blood Finally it must not under any circumstance be forgotten that common drugs such as the analgesics quinine salicylates and sulfonamides may produce scarlatiniform eruptions in those who suffer from an idiosyncrasy When the drug rash is accompanied by a drug fever the resemblance to an infectious disease is the more closely simulated

	DIAGNOSTIC FEATURES
Dermatitis Medicamentosa	A drug eruption following analgesics quinine salicylates arsenicals phenolphthalein, sulfonamides etc (p 3335)
Fourth Disease	Occurs in infancy Diffuse erythema of face body and extremities (p 418) No constitutional symptoms or lymphadenopathy Schultz-Charlton test negative
Erythromelalgia	Vasomotor neurosis of young and middle aged females Episodes of pain redness and swelling of hands and/or feet (p 1002)
Infectious Mononucleosis	Generalized lymphadenopathy (glandular fever) with characteristic hemogram (p 469) positive heterophile reaction (p 468) and false positive Wassermann (p 468)
Rubella	May produce scarlatiniform rash. Posterior cervical lymphadenopathy but mild constitutional symptoms rapid evolution and involution of eruption and negative Schultz Charlton (p 179)
Scarlet Fever	Acute erythrogenic streptococcal infection with fever sore throat and vomiting Initial eruption punctate followed by diffuse erythema and, later desquamation. Strawberry tongue Schultz Charlton blanching reaction (p 179)
Syphilis	Secondary syphilid with positive darkfield and serology (p 337)

valescent serum is injected intracutaneously If the rash is due to scarlet fever blanching should occur about the point of injection in from four to

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anti infective agent has no apparent effect on the toxic manifestations of the disease although it is successful in reducing the frequency and severity of complications Well controlled studies in moderately severe scarlet fever reveal that *antitoxic convalescent serum* and *sulfonamide* are about equally effective when used alone, the combination of sulfonamide with antitoxin or convalescent serum seems to be more efficacious than the use of any single modality

In scarlet fever, *sulfadiazine* is the preparation of choice as it is least likely to produce eruptions and is very mildly irritating to the urinary passages *Sulfapyridine* and *sulfathiazole* are contraindicated because of their nephrotoxic tendencies

The efficacy of *penicillin* remains to be established Since the modern variety of scarlet fever is mild and self limited it is difficult to evaluate the immediate efficacy of any specific therapeutic agent Statistical studies usually originate from institutions for contagious disease and do not include estimates of the long range ravages of the disease such as glomerulonephritis It is our own belief that penicillin should be given adequate routine trial for the dual purpose of its effect on the acute process and what is more important for its prophylactic value relative to complications It is within the realm of possibility that the prompt and effectual use of penicillin may reveal to the next generations of physicians a reduced incidence of late glomerulonephritis

Choice of Treatment in Private Practice—The practitioner has a variety of options in the management of scarlet fever He may elect to observe the spontaneous course of the disease he may give specific antitoxin or convalescent serum he may use sulfonamide or penicillin alone, in combination or in conjunction with serum

Because of the uncertainty of predicting long range complications of scarlet fever we oppose the principle of skilful neglect We are somewhat reluctant to advise the use of the *sulfonamides* since they are potentially toxic and preliminary trials fail to reveal any striking or specific therapeutic accomplishment We prefer the use of *convalescent human serum* to specific *heterologous antitoxin* on the basis that the former does not render the patient sensitive to horse serum We strongly favor injections of *penicillin* because of its vast potential and negligible toxicologic hazard

Ideally we advocate the immediate intramuscular injection of *penicillin* using an initial priming dose of 100 000 units with subsequent doses at four hour intervals of 50 000 units At the time of the initial penicillin injection an intramuscular injection of 20 to 100 cc of *convalescent human serum* is administered the dose being dependent upon the age of the patient and the severity of the symptoms If this preparation is not available 6000 U S P.H S units of *scarlet fever antitoxin* are substituted since the anti infective agent must be supplemented by an antitoxic substance if combined operations are to prove successful The repetition of the serum injection is dependent upon the clinical response, it may be given again at six, eight twelve- or twenty four hour intervals Penicillin injections must be maintained for a period of at least seven days

If penicillin cannot be given we favor the substitution of *sulfonamide* since the effect of this agent upon the incidence and severity of complications is far outweighed by the dangers inherent in its toxicology sulfa

immunity (p 185) In a patient with an erythematous rash the *Schultz Charlton test* (p 179) is often a diagnostic help Blanching which occur after scarlatinal antitoxin is injected into the site of the rash is presumptive evidence that the disease in question is scarlet fever If no blanching occurs the diagnosis of scarlet fever may be considered unlikely



A



B

Fig 19—Facial erysipelas A Third day B Sixth day

Treatment

The treatment of streptococcal infection differs only slightly from that of the staphylococcal invasions Nonspecific measures are utilized for the correction of obvious host defects such as metabolic disorders and for

Courtesy of Park Davis & Co

no erythema surrounding the puncture wound Erythema measuring 1 0 cm or more in diameter is considered *positive* indicating susceptibility In the most completely susceptible individuals the erythema may measure up to 4 cm in diameter (see Fig 10)

Active Immunization—Active immunity is produced by a series of injections of toxin in graduated doses While toxoids and whole bacterial vaccines have been tried from time to time only the *Dick toxin* is widely used at present for the production of active immunity It is given in 5 subcutaneous injections at weekly intervals Recently the Dicks have prepared toxin for oral administration but the effectiveness of this method *is not yet known*

TECHNIC—The *dosage of Dick toxin* is graduated beginning with 650 S T D subcutaneously followed at weekly intervals by a second dose of 2500 S T D a third dose of 10 000 S T D a fourth of 30 000 S T D and a fifth of 100 000 S T D A preliminary Dick test is performed and immunization is carried out only if it is positive If the Dick test is strongly positive (3 cm or larger) it is best to begin immunization with half of the usual first dose of toxin and then follow this in a week by the regular schedule of 5 doses as outlined above A few weeks after the last dose the Dick test should be repeated and if still positive (using 2 S T D intradermally) another dose of 100 000 S T D should be given subcutaneously

Immunization with Dick toxin also can be carried out by *intracutaneous injections* The usual 5 doses and the same total number of S T D are employed but the volume of material is only one tenth as large as by the subcutaneous route It is claimed that reactions are less common and immunity just as durable A further improvement in technic has been accomplished by the preparation of Tannic Acid Precipitated Scarlet Fever Streptococcus Toxin N N R Three weekly intradermal injections produce negative Dick reactions one month after completion of immunization

REACTIONS—*Local reactions* to the administration of toxin consist of swelling and redness over the site of injection and are rarely troublesome However about 10 per cent of persons develop general reactions These may be reduced in frequency and severity by adding 0 2 cc of 1 1000 epinephrine in the same syringe with the toxin before it is injected General reactions consist of fever malaise headache and vomiting and at times a light scarlatinal rash This is distinguished from true scarlet fever by the absence of a sore throat In addition urticaria may follow probably as a result of sensitivity to the broth in which the toxin is prepared Most persons who develop urticaria have previously been immunized with diphtheria toxoid which may contain similar protein material When purified scarlatinal toxin is employed this reaction is uncommon and can generally be controlled by epinephrine *Joint pains may also develop* after Dick toxin administration and are apparently the result of the toxin itself rather than impurities

RESULTS—Dick tests performed at intervals following active immunization show that 90 per cent of individuals retain their immunity for period up to twelve years About 10 per cent lose their immunity usually within a year after immunization There is no doubt that the incidence of scarlet

Unfortunately these same regulations are not applied to the clinically less severe manifestations of hemolytic streptococcal infection such as tonsillitis pharyngitis and otitis media Yet these minor infections are no less dangerous to the community than the others They are caused by organisms which differ in no way from the streptococci responsible for scarlet fever or puerperal sepsis From the point of view of community protection all group A strains of beta hemolytic streptococci are equally dangerous

Under ideal conditions patients with hemolytic streptococcal infections capable of being disseminated should be isolated Obviously no community can provide hospital facilities for this number of patients but that is neither necessary nor desirable In the hospital the patient is a menace to other patients and is himself in danger of contracting secondary infection with other types of hemolytic streptococci A start has been made in the control of hospital cross infections by methods aimed at the prevention of the air borne spread of organisms through sterilization by ultra violet ray and propylene glycol vapor (p 69)

The anti infective agents may be employed for prophylactic treatment in the management of contacts Penicillin in beeswax peanut oil may be given in single daily doses of 300 000 units by intramuscular injection or for oral use the preparation of choice is a sulfonamide preferably *sulfadiazine* which may be given in doses of 0.5 gm (7½ grains) four times daily In small communities prophylactic chemotherapy may be limited to direct contacts as in a classroom or a factory but in larger gatherings such as army encampments the entire population should be afforded the benefits of preventive treatment

SPECIFIC CLINICAL SYNDROMES DUE TO GENERALIZED STREPTOCOCCAL INVASION

In the special clinical syndromes of erysipelas septic sore throat scarlet fever and rheumatic fever the local manifestations of streptococcal invasion are of relatively lesser importance than the generalized disturbances due to toxemia bacteremia or perhaps a state of allergy

ERYSIPELAS

Erysipelas is an acute streptococcal infection of the skin and subcutaneous tissues characterized by sharply limited superficial erythema and usually accompanied by more or less severe constitutional manifestations

Etiology—The disease is caused by any one of the types of *Group A beta hemolytic streptococci* (p 159) The attack of erysipelas requires both predisposing and exciting factors since it is unlikely that even virulent organisms can invade the healthy intact skin Many individuals appear to have an unusual tendency to develop the infection and give histories of repeated episodes which usually follow minor trauma such as attempts to depilate nasal hairs picking the nose or clumsy attempts to remove blackheads by pressure of the finger nails The infection may be superimposed upon a laceration an open sore of any type or a surgical wound

Epidemiology—Erysipelas is quite prevalent and affects all ages and both sexes It is more common at the extremes of life and is observed in males more often than females In most instances infection is transmitted to susceptible individuals by *healthy carriers* When there are repeated attacks of erysipelas in the same individual it is likely that the

Etiology and Transmission —Septic sore throat is generally *milk-borne* The contamination of the milk results from infection of the cow s udder by a milk handler harboring hemolytic streptococci Since milk is a favorable culture medium for streptococci, the contaminated fluid contains enormous numbers of streptococci by the time the victim ingests it In contrast to the usual sporadic type of streptococcal pharyngitis and tonsillitis the severity of the disease and its short incubation period are explained simply on the basis of the great difference in the numbers of organisms introduced into the body

The infecting organism may or may not produce erythrogenic toxin This factor and the presence or absence of erythrogenic antitoxin in the serum of the patient determine whether or not a scarlatinal rash appears

Epidemiology —Epidemics of septic sore throat are usually explosive in character Epidemiological investigation reveals that the majority of patients use a common source of *unpasteurized milk* since the boiling or pasteurization of milk kills the invader

Clinical Manifestations —The *incubation period* of septic sore throat is short varying between one and three days The *onset* is rapid accompanied by chills high temperature and a rapid pulse The throat is beefy red and edematous The mucous membranes of the soft palate fauces tonsils and pharynx are hyperemic and deeply injected A grayish white or yellowish exudate is usually present on the pharynx and tonsils *Cervical lymphadenitis* is commonly present and the nodes are tender There is usually a *leukocytosis* of from 10 000 to 20 000 per cu mm with a predominance of polymorphonuclear leukocytes

Complications —The complications of septic sore throat are quite similar to those of scarlet fever (q v) as might be expected from the basic similarity of the two diseases *Otitis media suppurative lymphadenitis sinusitis* and *mastoiditis* are frequently encountered Late complications include *glomerulonephritis* and *rheumatic fever*

Diagnosis —The diagnosis of hemolytic streptococcal pharyngitis and tonsillitis generally can be suspected from the clinical appearance of the throat The membrane may be confused with that seen in diphtheria and Vincent s angina The differential diagnosis is made with certainty only by *throat smears* and *cultures* (p 50) The occurrence of multiple cases in a relatively short time immediately arouses a suspicion of septic sore throat

Treatment —Septic sore throat is a reportable disease Its management involves the same principles as those employed in the treatment of scarlet fever The use of the *sulfonamides* has proved to be somewhat disappointing and it is our belief that the initial preparation of choice is *penicillin* injected intramuscularly a sulfonamide particularly *sulfadiazine* may be given additionally if the symptoms are severe or the therapeutic response is not sufficiently rapid or satisfactory Should the patient exhibit a scarlatiniform eruption the administration of *convalescent human serum* or *scarlet fever streptococcus antitoxin* may be considered as in the treatment of scarlet fever itself In overwhelming protracted or seemingly resistant infection especially in the weakened the aged and the very young high concentrations of penicillin effected by massive dosages of 500 000 to 1 000 000 units daily or by the production of blockade (p 109) are worthy of earnest consideration

RHEUMATIC FEVER

Rheumatic fever is a disease characterized by febrile and toxic states by the presence of multiple disseminated focal inflammatory lesions in various parts of the cardiovascular system and joints and at times

Special Types of Erysipelas—*Recurrent erysipelas* is occasionally observed especially on the face The eruption is similar to that of acute erysipelas but the local reaction is generally less violent and constitutional symptoms are usually absent This type of erysipelas distinguished by its tendency to recur at the local site may be initiated by the most inconsequential trauma even exposure to wind and sun Eventually the recurrent and repeated inflammations lead to a state of chronic lymphangitis As a result of the lymph stasis (lymphedema) persistent and disfiguring swelling develops most commonly involving the cheeks nose and upper lids This *solid edema of the face* is more or less irreversible

Erysipelas is not infrequently superimposed on dermatophytosis of the toes (p 3298) This *erysipelatous dermatophytid* is essentially a secondary streptococcal cellulitis lymphangitis and lymphadenitis which begins in an area of dermatophytosis The patient complains of local pain and swelling The macerated area presents the usual features of an erysipelatous involvement or there may be the streaks characteristic of lymphangitis terminating in a reddened swelling in the region of the inguinal lymph nodes Constitutional symptoms are usually present and may be quite severe When this syndrome occurs repeatedly a chronic lymphangitis supervenes resulting in lymphedema and permanent swelling of the limbs

Constitutional Manifestations—The constitutional manifestations which accompany the skin lesions may be trivial or even completely absent but at the extremes of life and when patients are debilitated by chronic disease there is apt to be continuous or intermittent *fever prostration tachycardia headache* and *extreme toxemia*

Course—Since the introduction of the anti infective agents the unmodified course of the disease is no longer observed Prior to this life saving innovation an attack lasted from four to ten days and relapses were common

Involution begins in the region first involved so that the center of the lesion appears blanched while the margins are still red and actively inflamed As healing progresses the blebs dry and become encrusted and the skin desquamates in large thick flakes In the fatal case the lesion fails to involute and symptoms increase progressively until death occurs from complications toxemia or septicemia

Laboratory Findings—*Polymorphonuclear leukocytosis* is the rule the total count varying in most instances between 10 000 and 30 000 per cu mm of blood The lower counts are found in the less severely ill patients and also in those patients who suffer an overwhelming infection A feeble leukocytic response in an individual with severe toxemia and a spreading local lesion is a prognostic sign of gravest importance

Albuminuria and an occasional red cell in the urine occur almost as a routine The persistence of albumin or the appearance of a smoky urine caused by macroscopic *hematuria* points to renal involvement beyond the expected cloudy swelling *Bacteremia* occurs in the most severe infections

Differential Diagnosis—The differential diagnosis of erysipelas should offer little difficulty When the margins of the lesion are not sharply limited and raised there may be some confusion in distinguishing between erysipelas and cellulitis From a practical point of view this distinction is largely academic Both are streptococcal infections and require the same treatment

numerous cases of rheumatic fever This observation constitutes one of the strongest links in the chain binding rheumatic fever to the hemolytic streptococcus

Rheumatic fever is also a *crowd disease* it is more common in urban than in rural populations In cities it occurs among the poorer economic classes of society and it is quite uncommon among the well to-do It is probably activated by overcrowding malnutrition and poor sanitary conditions These factors render conditions favorable for the spread and maintenance of respiratory infections and thus indirectly favor the development of rheumatic fever

Rheumatic fever is most common in children of from five to fifteen years but no age group is immune to attacks of the disease Both sexes and all races are susceptible There is some suggestion that certain races are more susceptible than others and in New York City for example the disease seems particularly prevalent among Negroes coming from the West Indies

It is now quite clear that rheumatic fever is a *family* disease When one or both parents have had rheumatic fever the attack rates among the children are twice as high as in non rheumatic families and the evidence suggests that the familial prevalence of the disease is determined in part by hereditary susceptibility It follows therefore that the discovery of rheumatic fever in a child demands an examination of other members of the household



A



B

Fig 21 —*A* Aschoff body in the heart *B* Vascularization thickening and hyaline vegetation of mitral valve *

Pathology—The symptomatology of rheumatic fever can be better understood by a consideration of the nature of the pathologic processes involved in the disease The pathology of rheumatic fever consists of *exudative* and *proliferative* processes This is a distinction of more than academic importance since the exudative manifestations of the disease respond to salicylate therapy whereas the proliferative lesions are resistant

Exudative Lesions—The *acute* manifestations of rheumatic fever are characterized by a serofibrinous inflammatory exudate involving mesothelial surfaces and by vascular endothelial damage Engorgement of vessels and hemorrhage or diapedesis of red cells feature the early lesions There is also necrosis of collagen a finding which some observers regard as the essential lesion of rheumatic fever Exudative processes of this character account for such diverse manifestations as polyarthritis pleurisy pancarditis (pericarditis myocarditis and endocarditis) pneumonia peritonitis hematuria epistaxis iritis erythema marginatum purpura and urticaria

Proliferative Lesions—As the exudative lesions subside the more *chronic* proliferative lesions develop Of the latter the Aschoff body and the subcutaneous nodule are the most conspicuous The *Aschoff body* (Fig 21) is situated close to the adventitia of small blood vessels and is seen in most typical form in the interstitial tissue of the myocardium It may also be found in many other tissues of the body such as the aorta and visceral arteries The

* MacCallum Textbook of Pathology

Disturbance	Type of Lesion[1]	Herald Site	Spread	Duration from Evolution to Involution	Specific Features
Dengue	Macular	Dorsum of hands and feet	Extremities face and trunk	2 to 3 days	Epidemic
Measles	Raised macular and maculopapular (Fig 65 p 411)	Behind ears	Face neck trunk and extremities	3 to 10 days	Koplik spots on buccal mucosa (Fig 64 p 410)
Rubella	Maculopapular or erythema (Fig 66 p 417)	Face	Body and extremities	1 to 3 days	Postcerv lymph adenopathy
Fourth Disease	Diffuse erythema	Face	Body and extremities	2 to 3 days	Negative Schultz Charlton
Fifth Disea e	Macular	Face	Body and extremities	2 to 10 days	No Koplik spots
Sixth Disease	Erythema or maculopapular but not raised	Neck and trunk	Spares nose and cheeks	1 to 2 days	No Koplik spots Negative Schultz Charlton
Chickenpox	Macules papules and then vesicles (Fig 67 p 421)	Trunk	Head face and extremities	2 to 7 days	Pleomorphic[2] Monolocular[3]
Smallpox	Papular vesicular and pustular (Fig 68 p 424)	Forehead and wrists	Face arms trunk and legs	4 to 10 days	Monomorphic[2] Multilocular[3]
Infectious Mononucleosis	Macular papular erythematous or vesicular	Irregular	Irregular	Irregular	Lymphadenopathy Hemogram (p 469)
Dermatitis Medicamentosa	Macular papular vesicular urticarial (Fig 92 p 550)	Irregular	Irregular	Irregular	History of medication

NOTES

[1] The terms morbilliform scarlatiniform and rubelliform are avoided The morbilliform and rubelliform rashes are maculopapular scarlatiniform eruptions are first punctate and then erythematous

[2] Pleomorphic indicates that the individual lesions are simultaneously in different stages of evolution Monomorphic means that all are simultaneously papular vesicular or pustular

[3] Monolocular means the lesion can be evacuated by a single pin prick The multilocular vesicle or pustule cannot be emptied by a single puncture

toms in contrast to the *polycyclic* form in which the whole series of polyarthritis may be repeated one or several times There may be a *continuous* form of this disease in which low grade polyarthritis persists for months A diagnostic criterion of great value is the response of the arthropathy to *salicylates* While other joint disturbances such as gout are also relieved by *this group of drugs the infrequency of podagra in younger* persons results in a considerable specificity for the therapeutic test Despite the persistence of severe arthritis in rheumatic fever destructive changes in the joints do not occur

CARDIOPATHY —Cardiac involvement probably occurs in 95 per cent of patients afflicted with acute rheumatic fever The more closely the related evidences of cardiac damage are sought the more frequently they are found The development of ultimate permanent damage depends upon the severity of the involvement in the initial attack and the number and severity of recurrent attacks Tachycardia out of proportion to fever is perhaps the commonest early sign of rheumatic carditis Precordial pain and hyperesthesia *of the chest wall point to myocardial* as well as pericardial involvement Cardiac dilatation or pericardial effusion may be detected by daily examination and localization of the maximum cardiac impulse Poor heart sounds (embryocardia) gallop rhythm auricular fibrillation and other arrhythmias and systolic murmurs developing during the course of acute rheumatic fever point to cardiac involvement Manifest valvulitis and pericarditis are probably always associated with an underlying myocarditis The development of a precordial friction rub is pathognomonic of pericarditis

RESPIRATORY SYMPTOMS —*Acute serofibrinous pleurisy* is seen in 5 to 10 per cent of rheumatic patients It is characterized by sharp stabbing pain accentuated by respiration Later there may be respiratory embarrassment due to the mechanical effects of the accumulated fluid *Rheumatic pneumonia* occurs in a small number of the most severely ill patients and is manifested by transitory signs of consolidation developing in numerous areas of the lungs Pathologically there is an intense hemorrhagic edema somewhat resembling the fulminating pneumonias caused by the influenza virus

DERMATOSES —Various skin manifestations are observed during the course of rheumatic fever *Erythema multiforme* or *marginatum* is the most common but *purpura urticarial rashes* and *erythema nodosum* are also seen *Subcutaneous nodules* which develop from forty to seventy days after the onset of the attack are of prognostic importance since they tend to appear in the most severe cases *They are painless tiny nodules* from 1 0 to 10 mm in size and connected with the deep fibrous tissue The skin is freely movable over them

CHOREA —Chorea may occur in association with such severe manifestations of the disease as carditis or subcutaneous nodules In many other instances however it appears as the only manifestation of rheumatic fever

ABDOMINAL PAIN —Attacks of abdominal pain simulating acute appendicitis sometimes develop in the course of rheumatic fever and present difficult diagnostic problems Sterile hemorrhagic inflammation of the peritoneal surfaces is usually found when such patients are necessarily but erroneously explored

Disturbance	Constitutional Symptoms	Suggestive Objective Findings	Laboratory Data	Specific Tests
Infectious Mononucleosis	Mild to severe	Lymphadenopathy	Mononucleosis (p 469) False positive Wassermann (p 468)	Heterophile reaction (p 468)
Dermatitis Medicamentosa	None to moderate	None	None	None

DIFFERENTIAL DIAGNOSIS OF

The Commoner Generalized Afebrile Eruptions

Generalized eruptions associated with fever have previously been discussed The present concern is consideration of extensive rashes in the afebrile individual Some of these rashes as in syphilis represent a systemic infection despite the absence of disturbance of the temperature regulating mechanism other reactions are allergic (atopic dermatitis and dermatitis medicamentosa) The most frequently encountered rashes are the descriptive dermatoses (p 3355) of pityriasis rosea psoriasis and pemphigus

CAUSE	DIAGNOSTIC FEATURES
Atopic Dermatitis (Eczema)	An allergic reaction with itching erythema and vesiculation and scaling Frequent in infancy and childhood (p 3342)
Dermatitis Medicamentosa	Macular papular erythematous urticarial and pustular eruptions following analgesics sulfonamides quinine arsenicals iodides phenolphthalein, bromides gold salicylates etc (p 3335)
Exfoliative Dermatitis	Serious and often fatal peeling often following drugs particularly arsenicals (p 3383)
Frambesia Tropica	Extragenital crusted ulcer of primary lesion and generalized papular eruption Wassermann and darkfield positive (p 351) Favorable response to arsenicals
Generalized Vaccinia	Varioliform eruption following vaccination (p 433)
Molluscum Contagiosum	Virus infection causing umbilicated vesicles especially of face trunk and genitals
Pemphigus	Fatal bullous eruption of skin and mucous membranes (p 3405)
Pityriasis Rosea	Herald scaling patch followed by generalized itching macular eruption of trunk thighs and shoulders Self limited (p 3410)
Psoriasis	Chronic recurrent scaling and itching papules with predilection for elbows knees and extensor surfaces (p 3414)
Syphilis	Maculopapular vesicular or papular nonpruritic lesions Darkfield examination and serology positive (p 337) Specific responses to penicillin and arsenic
Xerosis	Dryness of skin and papules at mouths of hair follicles (keratosis pilaris) in vitamin A deficiency (p 3234) Specific response to therapy

DIFFERENTIAL DIAGNOSIS OF

The Commoner Febrile Skeletal Disorders

In the minds of the laity all inflammatory disturbances that involve bones joints muscles bursae or subcutaneous fibrous tissues are lumped together as rheumatism The following table gives only the commoner skeletal disturbances associated with fever Non febrile afflictions are listed later in the section devoted to Disturbances of the Skeletal and Locomotor System (p 2795)

CAUSE	DIAGNOSTIC FEATURES
Atrophic Arthritis	Idiopathic progressive polyarthritis of young adults Vasomotor instability Tendency to muscle atrophy with ankylosis (p 2910) All tests negative except sedimentation rate
Blood Dyscrasias	Fever with hemarthrosis or periostitis respectively in hemophilia (p 1118) or scurvy (p 1120) *Note capillary fragility in latter and response to vitamin C*
Bone Neoplasms	Fever especially with Ewing and osteogenic sarcomas (p 2845) X rays and biopsy positive
Brucellosis	*Arthritis and osteomyelitis may be acute subacute or chronic* Skin test Culture joint aspirate (p 314)
Dermatomyositis	Rare disease with skin and muscle lesions *Get blood culture and biopsy* Look for evidences of carditis (p 3373)
Gonococcemia	Pyarthrosis with or after urethritis Look for focus in prostate vesicles or uterine adnexa Get blood culture and complement fixation (p 219)
Gout	Polyarthritis sometimes with great toe involvement (podagra) in older males Look for tophi in ears Blood uric acid in excess of 5 mg Specific response to colchicine (p 2874)
Poliomyelitis	Epidemic virus disease with paralyses following prodromal febrile period. Get spinal fluid (p 3736) and examine blood for virus neutralizing bodies
Pyogenic Infection	Of joints and/or bones Obtain pus for smears and cultures in pyarthrosis Take x rays Make blood cultures in suspected bacteremia (streptococcus staphylococcus gonococcus meningococcus)
Rheumatic Fever	Polyarthritis or growing pains usually in children or young adults Seek evidence of carditis Note rapid sedimentation rate and specific response to salicylate (p 186)
Rickettsial Infections	Generalized myalgia but no localizing symptoms
Scarlet Fever	Arthralgia and occasional pyarthrosis in severe infections *Note rash or desquamation* (p 171)
Serum Sickness	Polyarthritis usually at time of urticaria (p 85)
Spirochetosis	*Arthralgia or serous effusion in infectious* jaundice and rat bite fever (p 365)

Clinical Manifestations.—The *incubation period* of scarlet fever varies from one to six days with an average of three to five days. The disease begins acutely with *nausea, vomiting, fever* and *sore throat*. The temperature generally rises rapidly to 101° to 104° F. Vomiting is one of the most constant of early symptoms.

The Exanthem.—Soon after onset there is a tendency for the face to become flushed and red, but the nose and mouth are spared so that a peculiar and characteristic *circumoral pallor* results. The *rash* appears from twelve to thirty six hours after onset. It may be generalized and prominent or so sparse and fleeting as to escape detection unless sought most carefully. The eruption appears first on the neck and chest, gradually spreading within twenty four hours to the arms and legs. It consists of numerous tiny red *maculopapules* appearing about the hair follicles. From



Fig. 90.—Scarlatinal angina (third day) (strawberry tongue).

their confluence the deep erythematous blush results. At times the individual punctate lesions resemble goose pimples in size. In mild cases the rash may be detected only in the folds of the axillae, elbows, groins and inner aspects of the thighs. The face is either spared or but minimally involved.

The Enanthem.—Quite as characteristic as the rash is the enanthem consisting of small bright red *hemorrhagic spots* on the *roof of the mouth* and *soft palate*. The *pharynx* and *tonsils* are diffusely hyperemic and edematous. Follicular or even confluent grayish white *exudates* may be present on the tonsillar and pharyngeal surfaces. In the most severe cases these exudates resemble diphtheritic *membranes* so strongly that only bacteriologic examination can separate the two conditions with certainty.

* Trumpp and Ibt

of years rather than of weeks or months Efforts that cease with the disappearance of the acute manifestations are doomed to tragic failure

Bed Rest—Since there is as yet no specific for the relief of the rheumatic infection, the therapeutic program is directed at palliative and symptomatic treatment The rheumatic child is confined to bed at absolute rest for an indefinite period During this time the generic treatment (p 68) for the infectious process is scrupulously followed Meals are served on a tray urinals and bed pans are used unless the child can be carried to and from the bathroom The difficulties of management are increased by the fact that rheumatic children require frequent bed baths and sponges since they perspire freely especially when they are taking salicylates Few physicians who have observed the untiring and heroic efforts of a mother to care for her afflicted child at home can fail to recognize the advisability of sanitarium treatment

Diet—During the period of bed rest a well balanced diet is recommended *Supplementary vitamin rations* are suggested Vitamin P obtained from red pepper and lemon peel is said to control the disease

It is important to instruct parents concerning food fallacies relative to rheumatic fever There is nothing to substantiate the belief that red meat is harmful or that fruit and fruit juices which are acid cause increased joint disturbances

Ultraviolet Radiation—If it is possible the child should receive ultraviolet radiation A portable source may be used the least expensive of which is the carbon arc lamp (p 3794) If this therapy accomplishes nothing else it gives the child an appearance of health The effect on morale cannot be overestimated

Local Measures for the Relief of Joint Pains—Painful joints should be treated by *local heat* Wrapping the afflicted member in cotton or flannel is the simplest device and *counterirritation* with oil of wintergreen *is very comforting* An improvised baking machine is *often most useful* for the treatment of the lower extremities (p 3787)

Relief from pain sometimes requires *immobilization* This is most easily accomplished by wrapping the affected part in layers of cotton and pinning an ordinary pillow over the entire dressing If this does not suffice a posterior molded splint may be tried

When the joints are tensely distended and refractory to simpler methods *aspiration* may provide instant relief and permit the physician to reduce the amount of sedative medication that had previously been administered Needless to state the strictest aseptic precautions are required in needling an inflamed joint *Local infiltration anesthesia* suffices for the introduction of the needle A *pressure bandage* should be applied immediately after the removal of the fluid to prevent recurrence

Salicylates—For the control of the *exudative manifestations* of acute rheumatic fever the drugs of greatest value are the salicylates (p 3833) and *aminopyrine* (p 3833). Their mechanism of action *is unknown* but their effects are often dramatic Within forty eight hours after adequate doses pain and swelling of the joints disappear fever is lessened and the symptomatic well being of the patient is greatly improved While joint exudates and pericardial effusions tend to subside under salicylate ther

fever than in any other acute infectious diseases In general the acute lesions occur more often in the severe varieties of the disease *Rhinitis* and *sinusitis* generally purulent are the commonest complications *Cervical adenitis* is the next most frequent but fortunately in only a small number of cases does it progress to the point of suppuration and abscess formation *Otitis media* is often observed and may be catarrhal or suppurative about a quarter of the latter cases progressing to *mastoiditis* Occasionally direct extension of the pharyngeal infection results in *peritonsillar* or *retropharyngeal abscess*

In addition to the complications due to extension of the infection distant toxic or metastatic lesions develop *Abscesses* occur in the subcutaneous tissues and *osteomyelitis infectious arthritis meningitis pericarditis endocarditis* and *myocarditis* add to the complexity and gravity of the disease

At the height of the febrile and toxic stage the majority of patients have albumin and casts in the urine In less than 3 per cent of all patients regardless of the severity of the initial disease an *acute hemorrhagic glomerulonephritis* develops from about the eighteenth to the twenty second day of disease There may be merely urinary findings of red and white cells with casts or in addition there may be edema hypertension oliguria and azotemia The frequency with which manifestations of *post scarlatinal nephritis* are recognized is proportional to the diligence with which they are sought (p 2373)

The *late sequels* of scarlet fever often present a difficult and baffling challenge to the practitioner The end stages of *glomerulonephritis* do not manifest themselves for years and even decades after the initial infection and as has been stressed they may as well follow the mild atypical and even subclinical hemolytic streptococcal infections as the frank ones Many patients who manifest idiopathic nephropathies and hypertension are probably members of this latter group The effect of chemotherapy on the chronic nephropathies will take many years to evaluate

Occasionally an attack of *rheumatic fever* may follow scarlet fever At times other acute infectious diseases including chicken pox and diphtheria occur during the course of scarlet fever These infections may develop a week or so after the onset of the primary disease so that the streptococcal exudate in the pharynx merges with the diphtheritic membrane

Diagnosis —In typical examples of the disease the clinical diagnosis of scarlet fever is not difficult The abrupt onset rapid development of fever headache vomiting and sore throat the appearance of the punctate eruption on the roof of the mouth and soft palate the involvement of pharynx and tonsils the strawberry tongue and the appearance of the rash followed by desquamation are characteristic features of the disease

Diagnostic difficulties are encountered in mild cases with *atypical* eruptions The localization of the rash in the folds of the axillae elbows and groins may be of differential value Of great help in diagnosis is a history of recent contact with a case of scarlet fever or other streptococcal infection The isolation of large numbers of hemolytic streptococci from the throat is also of presumptive diagnostic value

The *Schultz Charlton* or blanching test is of considerable assistance in diagnosis The technic of the test consists of the intradermal injection of

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eight hours The blanching is due to the neutralization of toxin by anti toxin (Fig 18 p 164)

Treatment —The treatment of scarlet fever requires rest in bed for at least two to three weeks after the onset even in the absence of complications While this precaution in no wise guarantees the avoidance of late complications it may perhaps reduce their severity and facilitate their early recognition

Symptomatic Treatment—The details of *symptomatic treatment* follow the general formula (p 68) Isolation is strictly enforced and local public health authorities are notified Dick tests are performed on contacts and preventive measures (p 183) are employed for the susceptible The dwelling is usually placarded The patient is isolated for a minimum of two to three weeks and longer if complications persist

Irrigations of warm isotonic glucose often afford considerable symptomatic relief from sore throat *Gargles* should not be given to small children because of the danger of aspiration of infective material into the glottis and eustachian tubes An *ice collar* or *warm applications* depending on preference afford symptomatic relief from cervical adenitis

Specific Serum Treatment—Specific therapy is available in the form of antitoxin and convalescent serum *Scarlet fever antitoxin* is best given intramuscularly in a single dose of at least 6 000 U S P H S units which may be repeated daily for three or more days if necessary When the full therapeutic dose of antitoxin is given on the first day of the rash spectacular results are often achieved The rash may fade within twenty four hours and the temperature may fall to normal Pain and inflammation of the throat subside and symptomatically the patient is greatly improved

Scarlet fever antitoxin is a form of horse serum Consequently foreign protein sensitization and serum sickness may result from its administration When the older forms of antitoxin were used serum sickness was often more severe than the original disease In recent years there has been a great improvement in the refinement and concentration of the product and as a result serum sickness occurs in only 1 or 2 per cent of patients and is generally mild Before antitoxin is administered due precaution must be taken to determine hypersensitivity (p 86)

Convalescent serum has enjoyed an increasing popularity in recent years Its chief practical advantage is that it is a homologous serum (human) and hence does not produce serum sickness It is of particular value in treating patients who are sensitive to horse serum Theoretically enormous doses would have to be given to equal the antitoxin content of commercial horse antitoxin but actually doses of from 20 to 100 cc are equivalent to the usual dose of antitoxin in therapeutic effect Convalescent serum has the additional theoretical advantage of containing anti bacterial antibodies as well as antitoxin The chief limitation to its more widespread use is the difficulty in obtaining an adequate supply Convalescent serum is given intramuscularly or intravenously Smaller doses (20 cc) are used for milder cases in small children Larger doses up to 100 cc are reserved for severer cases in adults

Anti-infective Therapy—Despite the promise with which the *sulfonamide drugs* were introduced in the treatment of scarlet fever the brilliant results of the drugs in erysipelas therapy have not been duplicated The

Biotherapy—*Streptococcal vaccine* and *antistreptococcal serums* have been employed many times and in almost infinite variations with uniformly disappointing results

Roentgen Therapy—Roentgen therapy has been tried for local joint manifestations and the treatment of the cardiac complications It is difficult to see how irradiation can be of any significant benefit

Anti histamines—The hypothetically allergic nature of rheumatic fever (p 187) suggests routine trial with anti histamine agents such as pyribenzamine 50 mg four times daily (p 565)

Hyperpyrexia—Particularly in chorea hyperpyrexia may be a useful form of treatment Certainly the other measures designed to have a specific effect on the rheumatic complications of the nervous system have been useless if not harmful These suggested efforts include repeated lumbar puncture autohemotherapy the use of nirvanol and hot or cold packs

In institutionalized children hyperpyrexia seems to shorten the course of the chorea and diminish its intensity The fever may be produced by intramuscular injection of boiled milk intravenous injection of typhoid vaccine or by the use of the hypertherm (p 3789)

Psychotherapy—The importance of supportive psychotherapy, in a protracted illness such as rheumatic fever cannot be overestimated It is necessary to maintain the morale of parents and child These efforts challenge the ingenuity and character of the best equipped practitioner As soon as possible children should be permitted to read and to become skilled in manual crafts The prospect of cardiac invalidism looms as a threat so great that it is essential for these children to be prepared to support themselves by skills or by some sedentary occupation in later life Schoolwork should be resumed as soon as possible and the child must be urged to keep up with homework Visits from the local clergyman the class teacher and schoolmates are often most welcome and can occasionally be arranged by a hint or suggestion from the attending physician The radio has done fine work in programs that are designed for shut ins'

Treatment of Circulatory Complications—The management of the circulatory complications secondary to rheumatic carditis is best considered in the chapter devoted to *heart failure* (p 920) However it might be well in this place to warn the practitioner against *the dangerous and needless use of digitalis* (p 854) unless definite indications for its administration are clearly demonstrable Digitalis despite its efficacy neither prevents nor relieves rheumatic carditis It should not be used as a prophylactic or merely because there are evidences of valvular involvement

Termination of Bed Rest—The termination of bed rest and attempted rehabilitation pose many difficult problems for the practitioner Premature restitution invites a recurrence while a protracted period of invalidism is debilitating, and may result in serious sequels (pp 3755 and 4120)

In order that the patient may be permitted to leave the bed the following minimum criteria are required normal temperature with daily fluctuations consistently less than 1 degree normal resting pulse rate normal erythrocyte sedimentation rate normal red and white blood counts and an appreciable and consistent gain in body weight When these conditions have been fulfilled the child may sit at the side of the bed with legs dangling for about ten or fifteen minutes Later he may be promoted to sitting

diazine is given orally in the dose of 2 to 4 gm (30 to 60 grains) depending on the age of the patient and the severity of the infection In overwhelming protracted or seemingly resistant infection especially in the weakened the aged and the very young high concentrations of penicillin effected by massive daily dosages of 500 000 to 1 000 000 units or by the production of blockade (p 109) are worthy of earnest consideration

There is little doubt but that this routine will require unnecessary and excessive treatment for a number of patients who might otherwise recover uneventfully without exposure to sensitization to horse serum or to the toxicity of the sulfonamide drugs On the other hand the practitioner has the satisfaction of knowing that he has given his patient the most effective available treatment If late subsequent sequels develop despite this he will have no cause for self reproach

Treatment of Complications—The complications of scarlet fever are treated symptomatically Conservatism is the rule referable to purulent conditions such as otitis media cervical adenitis and the like The introduction of anti infective agents has greatly reduced complications and *all* but eliminated the necessity for surgical intervention

When it has become apparent that drainage is required *specialist consultation* is needed for the ear throat or glandular affliction as the case may be Incision should be deferred if possible until the process has pointed so that liquid pus can be released with minimal operative trauma Local anesthesia is preferred because of the likely presence of virulent streptococci in the nasopharynx and the danger of aspiration Physicians and attendants require utmost precautions in handling scarlet fever patients lest they suffer cross infection or become carriers through misfortune or carelessness The practitioner who does obstetrics might well avoid contact with the disease in any form

Prophylaxis and Prevention—The prevention of scarlet fever by means of active or passive immunization is based upon attempts to produce immunity to the erythrogenic toxin of hemolytic streptococci The presence or absence of such immunity is determined by the Dick test

The Dick Test—The material for the Dick Test consists of the Berkefeld filtrate of broth cultures of erythrogenic strains of hemolytic streptococci The toxin is purified by fractional precipitation and dialysis so that the final product is obtained in a highly pure state Individuals whose blood contains no antitoxin react to the intradermal administration of toxin with the development of local erythema about the site of injection In persons who have antitoxic immunity no erythema results

While immunity to erythrogenic toxin is by no means an index of immunity to hemolytic streptococcal infection there is no doubt as to the efficacy of the Dick test as a means of differentiating those susceptible and not susceptible to the development of scarlet fever *with a rash*

The Dick test as now standardized consists in the intradermal injection of 0 1 cc of toxin containing 1 skin test dose (*S T D*) The latter is defined as the smallest amount of toxin which when injected into the skin of a known susceptible individual evokes a positive reaction The amount of protein in 0 1 cc of material is so small that false-positive nonspecific reactions are uncommon and control injection is not ordinarily necessary *The test is read in twenty four hours* To be considered negative there must be

tempted according to the following scheme from October to June during the period of high incidence of hemolytic streptococcic infection the pa tient is given daily 1 2 to 2 gm (18 to 30 grains) of *sulfadiazine* in four divided doses To prevent toxic manifestations one half to one level tea spoonful of bicarbonate of soda is administered with each dose of the drug and the bicarbonate sulfonamide combination is washed down in a full glass of water *Turbid urine specimens are examined immediately* a routine urine analysis is done at least at weekly intervals at which time a blood count is also made

Should the child develop hemolytic streptococcal infection or any type of upper respiratory inflammatory process either during the sulfonamide period or in the course of the rest of the year *salicylates* are administered following the demonstrable infection in the latent period preceding the ex pected attack of acute rheumatic fever There is abundant evidence to suggest that the salicylates inhibit the antigen antibody reaction that is responsible for the vascular and connective tissue injury in acute rheu matic fever *Sodium salicylate* in doses of 1 gm (15 grains) is ordered three or four times daily with bicarbonate of soda The drug is continued until toxic symptoms arise or until the latent period of ten days to two weeks has elapsed when sulfonamides may be resumed

Removal of Infected Foci—The prophylactic treatment of rheumatic fever has been attempted through surgical ablation of foci of infection The relation of focal infection in the upper respiratory passages to the per sistence and recurrence of rheumatic fever constitutes a debatable point concerning which there is no uniformity of judgment The opinions of many experts are diametrically opposed The enthusiasts for tonsillectomy and sinus exenteration favor routine ablation of any and every possible focus The conservatives point to statistical evidence that shows little beneficial result They point out further that subacute bacterial endocarditis some times follows tonsillectomy in cases of rheumatic heart disease This point is well taken The practitioner must not fail to precede tonsillectomy or even tooth extraction by a period of sulfonamide administration continued well into convalescence from the surgical procedure

We hold an intermediate position relative to ablation of foci of infec tion We are opposed to routine tonsillectomy in rheumatic as well as in healthy children but it is our opinion that the question of surgery should be considered on the individual merits of the given case We favor tonsil lectomy for children who give a history of exacerbations of rheumatic fever following upper respiratory infection and for those who have grossly in fected tonsils whether atrophic or hypertrophic We favor tonsillectomy for children who have had a peritonsillar abscess as well as the patient who is found to be a carrier of beta hemolytic streptococci Tonsillectomy and adenoidectomy are also indicated if there are evidences of interference with the airway by hypertrophied adenoid tissue or by enlarged faucial tonsils that meet in the midline We approve of intranasal surgery if gross pus can be demonstrated in any of the accessory nasal sinuses after several washings

Surgery in Cases of Rheumatism—The protracted course of rheumatic fever makes it inevitable that the problem of surgical interference should arise in the case of an afflicted patient just as it does in the normal The

fever is markedly less among immunized persons than among nonimmunized Dick positive individuals Nevertheless the procedure has not been adopted as widely as immunization to diphtheria The number of injections is large and the untoward reactions are numerous although with purified toxin they have been reduced Moreover scarlet fever today is a mild disease with an extremely low mortality rate Physicians are further deterred from the use of the method by the increasing realization as stated before that immunization only protects against the toxic manifestations of the disease but not against hemolytic streptococcal infections or the serious complications which may result from them

Passive Immunization—For the passive immunization of contacts exposed to scarlet fever antitoxin or convalescent *serum* can be used Since the incubation period of the disease is short and the diagnosis in the primary cases is rarely made until the rash develops these prophylactic agents are of little practical avail The shorter the interval between exposure and the administration of a prophylactic agent the greater are the chances of preventing the disease Although there is no strong evidence demonstrating the value of passive protection against scarlet fever it must be remembered in evaluating reports that the attack rate even among susceptible contacts is quite low

Antitoxin or convalescent serum should not be given indiscriminately to all contacts but only to those who are Dick positive as can be determined in eighteen hours Antitoxin is given intramuscularly in a dose of °000 U S P H S units (100 000 neutralizing units) after carrying out sensitivity tests Passive immunity does not last more than a week or ten days If further passive protection is desired convalescent serum rather than antitoxin should be given since the first dose of antitoxin sensitizes the patient to subsequent injections of horse serum Convalescent serum is given in amounts of from 16 to 30 cc intramuscularly and can be repeated without fear of sensitization

Prophylactic Use of Anti infective Agents—There is a real promise that the administration of the *sulfonamides* by mouth or injections of *penicillin* intramuscularly may prove of prophylactic value in susceptible contacts It will take considerable experience to establish this point one way or the other since the attack rate even among susceptible contacts is quite low and a large statistical experience will have to be obtained for more definitive information For the present however it would seem wise to give oral doses of 2 gm (30 grains) of sulfadiazine in four divided doses for several days to Dick positive children who have been definitely exposed to scarlet fever It is our impression that the ease with which this may be done provides one more argument against the more cumbersome method of active immunization

SEPTIC SORE THROAT

Septic sore throat is an acute epidemic disease caused by any type of Group A beta hemolytic streptococcus It is characterized by sudden onset with high temperature severe sore throat (with or without a membrane) cervical adenitis and considerable prostration It is distinguished from ordinary hemolytic streptococcal pharyngitis by its greater severity and its epidemic nature

Antigenic Structure —In contrast to the antigenic complexity of the streptococcus the structure of the pneumococcus is relatively simple The body and the capsule fractures may be considered separately

Somatic Fractions —The body contains one or more *nucleoprotein (P) fractions* common to pneumococci of all types and a *carbohydrate (C) fraction* The *somatic nucleoprotein* is antigenic but species-specific rather than type specific in that the antibodies produced against one type will react with the somatic proteins of all types Antisera produced by the immunization of animals with this fraction have no recognized therapeutic effect in the treatment of pneumococcal infection

The nature and significance of the *carbohydrate (C) fraction* are poorly understood A substance which precipitates with the C fraction can be detected in the blood and tissue fluids of patients early in the course of pneumococcal pneumonia but tends to disappear before or at the time of crisis Its persistence is a bad prognostic sign

Capsular Fractions —The type specificity of pneumococci is due to the presence of specific poly accharides in the capsule By appropriate chemical technics the capsular polysaccharides or *soluble specific substances* (S S S) have been isolated in highly purified form As far as has been determined each polysaccharide is chemically distinct for each type

Smooth and Rough Strains —When pneumococci are freshly isolated from human infections they are type specific encapsulated organisms which produce smooth colonies and are generally mouse virulent If the organisms are allowed to grow in the laboratory under unfavorable conditions and are not passed through animals they may become "rough (p 141) In this state the capsule is lost and the organisms are no longer type specific or mouse virulent There has been some speculation as to whether strains of pneumococci may change from one type to another by going through an S-R-S variation While this actually has been demonstrated in the laboratory there is no satisfactory evidence that the avirulent higher types of pneumococci common in normal throats may be converted by a process of mutation into virulent organisms of another type

Virulence —There is no evidence that pneumococci produce true *toxins* which contribute in any way to the pathogenesis of pneumococcal infections There is some evidence that *hemolysins* are produced as well as a substance which causes purpura when injected into mice but these substances do not play significant roles in human infection The polysaccharides isolated from the pneumococcus capsule are of the utmost importance in the pathogenesis of infection but are not, in themselves toxic These substances are soluble in the body fluids Their principal action as *aggressins* (p 145) is the neutralization of the specific antibody that is naturally present or supplied in the form of anti-pneumococcus serum By neutralizing or combining with antibody the soluble polysaccharides prevent the agglutination and phagocytosis of the organisms themselves Pneumococcal infection therefore must be regarded as the result of invasion by the whole organism rather than by toxic fractions or true exotoxins

Pneumococci are virulent for a variety of laboratory animals Lobar pneumonia has been reproduced in dogs rats and monkeys by the intratracheal or intrabronchial injection of virulent pneumococci Rabbits develop a septicemia when injected intradermally or subcutaneously with virulent strains In mice intraperitoneal injection is followed by blood stream invasion and death from septicemia Because of their cheapness and convenience in handling mice are used routinely for the isolation of pneumococci from sputum and other material and for the standardization of antipneumococcal serum Only encapsulated typable pneumococci are mouse virulent and all types are not uniformly virulent Some of the higher types of pneumococci are entirely avirulent for mice or will kill the animals only when very large numbers of organisms are injected There is no strict correlation between human virulence and mouse virulence For example pneumococcus Type XIV is virulent for man and is a common cause of pneumonia especially in children but it is largely avirulent for mice

Types of Pneumococci —The great majority of pneumococci are divisible into different types numbered from I to XXXII Type XXVI is identical with Type XVI and Type XXX is the same as Type XV but with these exceptions the remaining types differ from one another in virulence and are distinguished by possessing a capsular polysaccharide which so far as is known is distinct for each variety In addition to these main types more than forty other varieties of pneumococci have been recognized For one of them Type XXXIII a specific antiserum has been produced The others occur so infrequently that they are of little practical importance unless a strain is encountered which does not react with the diag

by serofibrinous inflammation of some of the great mesothelial lined body cavities and joints While the etiology of rheumatic fever is as yet unknown there is increasingly strong evidence that infection with hem olytic streptococci plays an essential role in the initiation of the disease and the development of recrudescences

Acute rheumatic fever is a disease which seeks out those in the poorer economic levels of society Its incidence in the United States is high and it has a tendency to strike and cripple children and young adults who should be at the peak of productive efficiency Public health authorities have recognized the magnitude of the rheumatic fever problem and an increasing number of public projects is devoted to the study treatment and prevention of this crippling disease

Etiology—From time to time different workers have laid claim to the discovery of the etiologic agent of rheumatic fever Among such alleged agents are various filtrable viruse and organisms of the pleuropneumonia group Without going into detail none of these claims has been substantiated There can no longer be any doubt that the hemolytic streptococcus has some intimate relationship to the development of the initial and recurrent attacks of this disease Evidence in support of this view is afforded by the detection of several types of antibodies following known infections with the organism Specific antistreptolysins and antifibrinolysins which have been most extensively studied develop in the blood of 90 per cent of non rheumatic subjects convalescent from scarlet fever erysipelas and other hemolytic streptococcus infections These patients develop particularly high titers of antistreptolysin O in their sera In a like manner following the onset of an initial attack of rheumatic fever 90 per cent of rheumatic patients develop high titers of antistreptolysin O and this occurs regardless of whether or not the patients give a history of an upper respiratory infection preceding the onset of the rheumatic fever Similarly 75 per cent of recurrent attacks of rheumatic fever are accompanied by a rise in antistreptolysin O titer Since it is generally agreed that such immunological reactions result only from hemolytic streptococcal infections the conclusion is inescapable that *rheumatic fever is associated with caused or precipitated by hemolytic streptococcal infection* (p 157)

The mechanism by which rheumatic fever is induced by streptococcal infections is obscure The latent period of ten days to two weeks between the streptococcal infection and the onset of the exudative phase of rheumatic fever strongly suggests an allergic or hyper sensitive reaction and this is the hypothesis most widely favored On the other hand streptococcal infections may equally well serve to activate a hypothetical rheumatic "virus" or perhaps lower the resistance of the body to such a virus" The analogy of febrile diseases activating the herpes simplex virus comes to mind Further evidence of the relationship of hemolytic streptococcus to rheumatic fever is considered in discussion of the epidemiology of the disease

Epidemiology—Rheumatic fever is not a reportable disease so that accurate statistics as to its prevalence are not available There can be no doubt however that it ranks among our most important chronic diseases About 2.5 per cent of the total number of patients admitted to general hospitals in this country have rheumatic fever and in children's hospitals the rate is 5 6 per cent In some sections of the country the total mortality from rheumatic heart disease *is exceeded among infectious diseases only by tuberculosis lobar* pneumonia and syphilis Surveys among school children in several large eastern cities show that between 0 6 and 1 6 per cent have cardiac lesions 80 to 90 per cent of which are probably rheumatic in origin

There is general agreement that the disease is common and severe in temperate zones less common in warmer and subtropical climates and rare in the tropics In American Indian children the disease is ten times as prevalent in the northwestern as in the southwestern states

Rheumatic fever is distinctly a *seasonal disease* The greatest incidence of attacks is in the late winter and early spring which corresponds to the seasonal prevalence of scarlet fever and hemolytic streptococcal infections in general Epidemic occurrences of rheumatic fever have been observed in relation to epidemics of streptococcal disease Several recent epidemics of septic sore throat and scarlet fever have been accompanied or followed by

sometimes useful in evaluating the prognosis and response to specific therapy This is considered in detail elsewhere (p 2175)

Blood Cultures—For the detection of pneumococci in the blood stream 5 cc of venous blood are inoculated into a flask containing 100 cc of beef broth and incubated at 37 C When pneumococci are present growth is usually evident within twenty four hours as indicated by a purplish discoloration of the medium after the flask has been agitated Positive cultures are typed by the Neufeld method

Antibodies to the Pneumococcus—Most individuals possess some degree of *natural immunity* to pneumococcal infection This is indicated by epidemiological observations of the sporadic nature of the disease and can also be shown by immunological tests *Opsonins* and *bactericidins* often to a considerable degree are present in the blood of many normal adults One cubic centimeter of blood of many *normal persons* can kill more than 1000 pneumococci.

Recovery from pneumococcal infection depends ultimately on *phagocytosis* and the most important cell in this mechanism is the wandering *macrophage* It is often necessary or desirable in the course of treatment of pneumococcal infections especially after the administration of anti pneumococcal sera to test for the presence of *humoral antibodies* They ordinarily develop at the time of crisis both in untreated patients and in those treated with sulfonamide drugs They may be induced passively by the administration of anti pneumo-

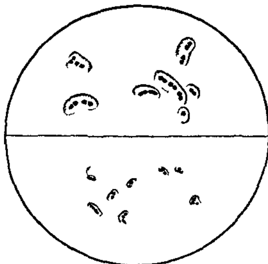


Fig 2?—Quellung of pneumococci *

coccal serum These antibodies are type specific and are demonstrated only with the use of homologous pneumococci The first to appear in point of time after the onset of infection are *bactericidins* and *opsonins* whose demonstration is technically difficult The next antibody to appear is the *type specific agglutinin* which when present indicates a considerable concentration of type specific antibody in the patient s serum

Demonstration of Agglutinins—Type specific agglutinins are simply and readily demonstrated by the *slide agglutination technic* To perform this test a drop of broth culture of pneumococci previously isolated from the patient is mixed on a glass slide with a few drops of the patient s blood serum The preparation is dried in air fixed with heat and stained by Gram s method When examined under the microscope the pneumococci will be seen aggregated in large clumps if the serum contains type specific agglutinins When a high level of antibody is present in the patient s blood capsule swelling may be demonstrable by the Neufeld technic using the patient s serum instead of diagnostic typing sera

Francis Test—The presence of antibody may also be shown by a skin test devised by Francis If the patient has developed type-specific antibodies to the homologous organism the intradermal injection of type specific polysaccharide will produce a positive skin reaction

* Jordan and Burrows Textbook of Bacteriology

center of the lesion consists of necrotic collagen surrounded by large multinuclear epithelioid cells with dark basophilic cytoplasm Lymphocytes plasma cells polymorphonuclear leukocytes and fibroblasts complete the Aschoff body *Subcutaneous nodules* are rheumatic granulomas consisting of groups of modified Aschoff bodies The early lesion of rheumatic endocarditis is probably an interstitial exudative inflammation which later becomes proliferative The characteristic verrucae of the cusps develop secondarily

The varied symptomatology of rheumatic fever is easily correlated with the diffuse nature of the exudative phase of the pathological process while the late results are due to progressive damage to the heart in subsequent recurrences of the disease

Brain Lesions—In fatal cases of *chorea* the brain shows perivascular collections of round cells and endothelial proliferation in the meninges cerebral cortex and corpus striatum Although the pathology of chorea is not similar to that of the rheumatic process elsewhere it must be considered that the histological structure of the brain makes it respond differently than other tissues

Clinical Manifestations—The manifestations of acute rheumatic fever may be slight and insidious or frank and obvious There is strong likelihood that *subclinical* rheumatic fever occurs with much greater frequency than the manifest variety It offers the greatest difficulty in diagnosis as evidenced by the appreciable number of rheumatic cardiac invalids who have no certain knowledge of the acute episode which led to their difficulties or who presented such equivocal manifestations of the infection as to completely escape or mislead the attending physician

Subclinical Rheumatic Fever—The subclinical manifestations of the disease include a failure to gain weight anemia frequent respiratory infections low grade joint aches (characterized as *growing pains*) a slight tachycardia and a low grade pyrexia which is observed only when rectal temperatures are taken at four hour intervals over long periods of time The fever may be relative rather than absolute (p 22) These inappreciable and easily overlooked symptoms and signs may represent the insidious onset of a crippling disease The astute practitioner who is more apt than his colleague in institutional practice to see this phase of the disease should be ever on the alert to recognize and evaluate such disturbances

Overt and Manifest Acute Rheumatic Fever—Overt or manifest acute rheumatic fever is usually preceded by an upper respiratory infection due to the hemolytic streptococcus The acute exudative phase develops after a latent period of one to three weeks The symptoms may be of protean character There may be fever tachycardia prostration epistaxis or other hemorrhagic manifestations and finally polyarthritis Despite the usually prominent association of arthritis with rheumatic fever joint manifestations may be completely absent or fleeting and transitory

ARTHROPATHY—In typical instances the arthritis of rheumatic fever is *migratory* and affects chiefly the *larger joints* The involved knees ankles wrists elbows or shoulders are red swollen hot and tender The pain is due in part to the pressure of the accumulated synovial fluid but involvement of the periarticular structures is also an essential feature of the lesion The joint fluid is sterile as are the other serofibrinous exudates in mesothelial lined cavities of the body The swelling in any given joint usually subsides in four or five days after which another joint becomes involved The whole cycle of polyarthritis lasts several weeks

In *monocyte* forms of the disease there are no further joint symp-

Clinical Manifestations of Pneumococcal Infection

The clinical manifestations of pneumococcal infection include primary and secondary local inflammatory processess pneumococcemia and metastatic involvements the most frequent of which is lobar pneumonia

PRIMARY AND SECONDARY LOCAL INFECTIONS

Local infections with the pneumococcus may be primary or complicating *Pneumococcal conjunctivitis* (p 1620) is usually primary but the role of the pneumococcus in upper and lower respiratory infections appears to be less certain There is much evidence to sustain the view that *nasopharyngitis tonsillitis pharyngitis sinusitis otitis media* and *pneumonitis* are of primary virus origin with the pneumococcus as a secondary invader *Pneumococcal meningitis* is invariably secondary and follows skull fracture ear or nose infections (p 2128)

PNEUMOCOCCEMIA

Pneumococcemia may or may not be preceded by a recognized local infection though it is quite probable that some portal of entry is always present A positive culture may be demonstrated in a high percentage of patients with *lobar pneumonia* early in the course of the disease The bacteremia probably precedes the pulmonary localization and persistence of the organism in the blood stream beyond the third fourth or fifth day indicates *a grave prognosis and suggests that some type of metastatic involvement* may be present (p 2171)

METASTATIC INFECTIONS INCLUDING LOBAR PNEUMONIA

Pneumococcemia may be followed by localization of the organism in some distant tissue In this way the patient may give evidences of a pneumococcal *arthritis, osteomyelitis peritonitis meningitis pericarditis endocarditis* or *lobar pneumonia*

Pneumococcal Lobar Pneumonia—It would be consistent to discuss pneumococcal lobar pneumonia in the present section the pulmonary lesion is usually if not invariably preceded by pneumococcemia and treatment is conducted by the systemic use of the anti infective agents Nevertheless we have transferred the descriptions of lobar pneumonia to the section on the Respiratory Diseases (p 2013) since other organisms may cause the pneumonic lesion and the pneumococcus may produce other types of inflammation in the respiratory tract

See *Differential Diagnosis of Commoner Febrile Skeletal Disorders* (p 192)

Specific Treatment of Pneumococcal Infection

The specific treatment of pneumococcal infection may be described as an embarrassment of riches Immunotherapeutic and anti infective agents are all highly efficacious

Local Treatment—Specific treatment for local pneumococcal infection is particularly useful in conjunctivitis (p 1620) The available agents include *ethyl hydrocupreine (optochin) the sulfonamides tyrothricin* and *penicillin* There is now general agreement that the topical application of *optochin* is most disappointing and certainly not comparable to the efficacy of the more recently introduced remedies As in most other instances where

Course—The course of rheumatic fever is variable and unpredictable All of the frank symptoms are rarely seen in any one attack A patient may have some of them during one attack and others during recurrences Rheumatic fever frequently runs a course so insidious that when the patient finally presents himself with obvious organic heart disease he can give no clear history of preceding rheumatic fever In children polyarthritis and the other frank exudative lesions are less common while carditis is often the most prominent feature of the disease In some patients only the vaguest manifestations of the disease such as failure to gain weight anemia and low grade joint pains constitute the conscious registration of a profound affliction

Diagnosis—There are no specific tests available by which the diagnosis of rheumatic fever can be made with certainty In this disease perhaps more than any other diagnosis rests upon a *complete evaluation* of the history physical findings course and laboratory studies

Leukocytosis of from 10 000 to 20 000 cells per cu mm with a predominance of polymorphonuclear leukocytes is characteristic of acute attacks When rheumatic fever smolders the white count may be but slightly elevated *Fever* is invariably present during the stages of frank activity but in subacute stages the temperature may be normal or exhibit only slight fluctuations in relation to exercise

The *erythrocyte sedimentation rate* (p 3707) is elevated during activity Its frequent determination is of distinct value in deciding the difficult question of whether or not the process is still active The *electrocardiogram* shows a prolongation of the P R interval during active carditis Persistence of this abnormality indicates continuing activity *Moderate secondary (hypochromic) anemia* refractory to iron therapy likewise raises the suspicion of continuing rheumatic activity The antistreptolysin titer at the present time is a research tool of little practical importance in the management of the disease A *definite response to salicylates* is of considerable aid in making a presumptive diagnosis of rheumatic fever

The diagnosis of rheumatic fever is difficult at best and when the manifestations of the disease are vague and indefinite the problem becomes one of opinion and judgment Under these circumstances the physician owes it to the patient and to himself to inform the parent or guardian of his suspicions The weight of the opinion of a consultant is often a consolation in later years and should be suggested by the practitioner Because of the dire consequences of neglect in diagnosis and treatment it is wiser for the practitioner to err on the side of being too inclusive in his diagnosis It is better to *suspect the presence of the disease too frequently than too seldom*

Complications—The rheumatic invalid has not only to contend with the ravages of the acute infection but he is under the constant threat of the superimposition of a *subacute bacterial endocarditis* involving the already damaged heart valves This complication which may be caused by alpha or gamma streptococci the influenza bacillus and other feebly pathogenic organisms is always to be suspected when the febrile course persists and the progress of the patient is steadily downhill The appearance of petechiae Osler Janeway nodes a palpable spleen tenderness of the sternum a cafe au lait color clubbing of the fingers and toes or a

n is encountered If the patient has to be treated by the oral route *lfadiazine* is the product of choice with *sulfamerazine* as an alternate For e mild or moderately severe attack the initial dose is 4 to 6 gm (60 to grains) for the adult of average size with 1 gm (15 grains) doses at ır hour intervals thereafter until the infection has become well con olled If the patient is more critically ill and a higher level of sulfonamide the blood is desired the initial dose is 6 to 8 gm (90 to 120 grains) and bsequent doses of 1 gm may be given at three hour intervals As in all ier instances of sulfonamide therapy each dose is accompanied by ½ 1 teaspoonful (2 to 4 gm) of bicarbonate of soda and a full glass of iter or other fluid (p 88)

If parenteral administration is desired the practitioner has his choice an intravenous injection of 5 gm of *sodium sulfadiazine* administered in per cent or 25 per cent solution or of intramuscular or intravenous *nicillin* Our preference under any circumstance is for the intramuscular iection of penicillin employing 100 000 units for the initial dose and 000 units for the subsequent doses given at three- or four hour ervals Our choice of penicillin is based essentially upon the lesser danger toxicity (p 109) the fewer encounters with resistant bacteria and the

TABLE 19 —SULFADIAZINE DOSAGE IN TREATMENT OF PNEUMOCOCCAL PNEUMONIA IN CHILDREN

Age	Initial Dose	Maintenance Dose
Under 6 months	0 5 gm	0 25 gm every 6 hours
6 mos to 3 years	1 0 gm	0 5 gm every 6 hours
3 to 10 years	2 0 gm	1 0 gm every 6 hours

eat certainty of its remediable effects In overwhelming protracted or emingly resistant infection especially in the weakened the aged and the ry young high concentrations of penicillin effected by massive daily sages of 500 000 to 1 000 000 units or by the production of blockade (p 9) are worthy of earnest consideration

The critically ill patient should be given the advantage of both agencies e sulfonamide may be given by mouth or intravenously and the penicillin ramuscularly or intravenously Most powerful effects can be obtained if intravenous drip is established with penicillin and sodium sulfadiazine ded alternately every two hours to the infusate

If either one of the drugs is used separately and a distinctly beneficial ect is not obtained within twenty four or thirty six hours the addition substitution of the other is worthy of consideration holding type specific novalent antipneumococcic serum for the third choice in the rare event it both anti infective agents prove unsuccessful In addition to systemic e penicillin should be injected *intrathecally* in meningitis using 50 000 its in 2 cc at least once daily and intrapleurally in empyema thoracis 2222)

The dosage of sulfadiazine in the treatment of pneumonia in infants and ildren is given in Table 19 (after Hodes)

Systemic Mycoses	Destructive arthritis and/or osteomyelitis may be acute subacute or chronic Lumpy jaw in actinomycosis (p 489) Desert rheumatism in coccidioidomycosis (p 499) Lesions also in histoplasmosis (p 504) Identify organisms in joint fluid or biopsy Skin test for coccidioidomycosis
Syphilis	Polyarthritis in secondary stage with positive serology (p 337) Charcot joint with painless destruction in tabetics with positive spinal fluid (p 1466)
Trichinosis	Nematode infestation with myalgia eosinophilia and swellings under eyes Skin test and complement fixation (p 539)
Tuberculosis	Arthritis or osteomyelitis with extensive destruction of bone and minor inflammatory evidences (cold abscess) May break through and dissect producing Pott s abscess of soft tissues X ray for evidences of pulmonary or renal lesion and to determine extent of local lesion Do skin test and sedimentation rate (p 252)
Typhoid Fever	Osteomyelitis with bone abscess May occur long after subsidence of acute infection Culture bacillus from pus (p 54)
Virus Infections	Generalized myalgia arthralgia and/or ostalgia but no localizing signs in common cold influenza dengue measles smallpox, choriomeningitis psittacosis sandfly fever and yellow fever (p 387)

sudden anemia indicates the necessity for taking a blood culture which often must be repeated several times and observed for several weeks before the organism can be made to grow out

The entire subject of subacute bacterial endocarditis is discussed under Diseases of the Circulatory System (p 1091)

Prognosis —While death is a relatively uncommon eventuality of an acute attack of rheumatic fever there are few diseases which carry so *ominous a prognosis* One attack of rheumatic fever predisposes to others which are usually precipitated by infections with the hemolytic streptococcus Repeated infections even of the subclinical variety may carry an ultimate prognosis of chronic cardiac invalidism and later death from circulatory failure

The practitioner has only a few signposts by which he may guide his prognostication The outlook is distinctly poorer when the attack occurs *early in life* A study of a thousand selected patients with rheumatic fever occurring in childhood revealed that 25 per cent were dead within ten years after the first attack In older patients polyarthritis is the more outstanding manifestation of the disease and the prognosis for cardiac invalidism is not as ominous as in children

Active Treatment —In the active treatment of rheumatic fever as in tuberculosis the practitioner is confronted with the long range problem of the control of a smoldering infection that continues to burn over periods

CHAPTER 5

COCCAL INFECTIONS NEISSERIACEAE

Meningococcus (*N intracellularis*)
Gonococcus (*N gonorrhoeae*)

MENINGOCOCCUS

Neisseriae —Meningococci are members of the *Neisseriae* a group of gram negative cocci occurring in pairs tetrads or small clumps Other important members of this group include the *gonococcus* *N catarrhalis* *N pharyngis sicca* *N flavescens* and the *Diplococcus crassus* These organisms are parasitic on human tissue and man is their chief if not their only natural host Their disease producing capacities vary greatly The meningococcus and gonococcus are pathogens whereas the others are generally innocuous inhabitants of the nasopharyngeal mucous membrane These organisms are morphologically quite similar and with the exception

TABLE 20 —BIOLOGICAL PROPERTIES OF NEISSERIAE

	DEXTROSE	MALTOSE	LACTOSE	SUCROSE	GROWTH ON PLAIN AGAR	GROWTH AT 22 C
Neisseria meningitidis	+	+	0	0	0	0
Neisseria gonorrhoeae	+	0	0	0	0	0
Neisseria catarrhalis	0	0	0	0	+	+
Neisseria pharyngis sicca	+	+	0	+	+	+
Neisseria flavescens	0	0	0	0	Poor	[illegible]
Diplococcus crassus	+	+	+	+	+	+

* This organism produces a golden yellow pigment

of the gonococcus may be cultivated from the upper respiratory tract In general a gram negative diplococcus isolated from spinal fluid in a clinical case of meningitis may be regarded as a meningococcus and a morphologically similar organism present in the discharges from an acute purulent urethritis is a gonococcus From blood cultures both meningococci and gonococci can be isolated

The separation of the different members of the Neisseriae is a technical problem for the expert requiring observations of growth requirements as regards media temperature carbon dioxide tension pigment production fermentation of selected sugars agglutination in normal horse serum and specific serologic reactions Some of these differences are summarized in Table 20

Bacteriology of the Meningococcus —In 1887 Weichselbaum clearly identified the *Diplococcus intracellularis meningitidis* as the causative agent of epidemic cerebrospinal meningitis (Fig 8) In spinal fluids obtained from patients with meningococcus meningitis the organisms appear within the cytoplasm of leukocytes or extracellularly as gram negative *diplococci* The two cocci in the pair are rounded with their adjacent sides somewhat flattened

apy these drugs have no effect on the proliferative lesions of the disease which continue to progress Subcutaneous nodules develop in children who have been under continuous salicylate therapy since the beginning of the attack

Either *acetylsalicylic acid* or *sodium salicylate* may be used The latter is preferably given with equal quantities of sodium bicarbonate From 7 to 10 gm (105 to 150 grains) in divided doses throughout the day are administered until the patient is saturated with the drug The dose is then cut down as individually required until it is large enough to suppress the joint symptoms but too small to produce toxic symptoms which include the well known manifestations of *salicylism* (p 3834) such as nausea and vomiting tinnitus and deafness The tendency of salicylates to produce gastric distress is especially unfortunate and confusing in children with rheumatic carditis in whom similar discomforts may arise as a result of cardiac decompensation or digitalization

For those patients who *cannot tolerate salicylates aminopyrine is* the drug of choice Children should be given 1.5 to 2 gm (22½ to 30 grains) a day and adults 2 to 3 gm (30 to 45 grains) a day The total dose is divided throughout the twenty four hours Aminopyrine is practically without effect on the gastro intestinal tract but may produce *agranulocytosis* (p 1096) hence frequent white blood counts are mandatory Should the leuko cytes fall below 4000 to 5000 per cu mm the drug must be discontinued

Salicylates or aminopyrine are continued as long as evidences of rheu matic activity persist Too hasty withdrawal results in a return of symp- toms On the other hand it is impossible to consider the disease inactive while the patient is still taking antirheumatic drugs since they tend to suppress fever tachycardia and joint symptoms The patient must be observed and studied for a period of time after the withdrawal of these drugs in order to be sure that the disease is really quiescent The intra venous use of salicylate previously regarded as prohibitively dangerous has been revived using the drip method The introduction of 10 gm of the sodium salt in 2000 cc of saline solution effects a plasma concentration in excess of 350 gammas per cc and appears to cause prompt subsidence of clinical signs as well as prevention of cardiac damage Massive salicylate therapy is not recommended for routine use as fatal poisonings have been reported

The rectal use of salicylates has been suggested because of the mistaken notion that nausea and vomiting result from local action whereas all the available pharmacological data point to a postabsorptive mechanism for the production of toxic symptoms Many variations in salicylate therapy have been suggested including the use of more expensive salts such as *strontium or the so called natural sources in place of the synthetic* Perhaps the only variant that has any value is an *effervescent salt* which acts more promptly and may produce less gastric irritation

Anti infective Agents—Neither the *sulfonamides* nor *penicillin* have produced beneficial results in the treatment of the acute phases of rheu matic fever Penicillin is at least innocuous but the *sulfonamides* appear at times to aggravate the rheumatic manifestations and their toxicologic phe nomena particularly the rashes may cause great confusion

genically homogenous mouse virulent encapsulated form halos and give positive precipitin reactions with group-specific rabbit antisera prepared against them

Group II strains have been isolated in inter-epidemic years from sporadic cases of meningitis They are often found in carriers except during epidemic periods Group II strains in general are heterogenous and less virulent for mice With the exception of the II A strains they do not have capsules and do not show halo reaction Polyvalent antimeningococcic serum usually contains few antibodies specific for Group II organisms which may in part explain the failure of antimeningococcus serum in the treatment of certain infections

Toxins of Meningococci—Meningococci readily autolyze in culture and produce *endotoxins* which in large doses are lethal for laboratory animals In addition to endotoxins an *exotoxin* which is probably antigenic can be obtained by a special technic from filtrates of young meningococcus fluid cultures *Antitoxin* prepared against this substance has been used with apparent beneficial results in the treatment of meningococcus infection

Epidemiology—Meningococcus meningitis occurs both sporadically and in epidemic form In non epidemic years there are from 3000 to 5000 cases reported annually in the United States Even in epidemics the attack rate is not high as illustrated by the experience of the United States Army during World War I during which time only 5838 cases were reported although meningococcus meningitis was epidemic During the 1940 epidemic in England which was considered quite extensive somewhat more than 10 000 cases occurred This is in marked contrast to the high attack rates characteristic of respiratory diseases such as measles and influenza Meningococcus infection occurs in all age groups but is most common in children The mortality is highest in young infants lower in children and young adults and then rises progressively with advancing age

Since meningococcus infection is transmitted by way of the nasopharynx it is most common during winter and early spring when respiratory infection in general is most prevalent The organisms are transmitted from the nasopharynx of a case or carrier to the upper respiratory tract of contacts directly or by air borne droplets

Meningococcus infection is an outstanding example of a disease in which the reservoir of infection is the *healthy carrier* Even in epidemics it is rare for meningitis to develop among the immediate contacts In non-epidemic periods surveys show that from 2 to 8 per cent of normal persons carry the organism in the nasopharynx These findings can be explained in either or both of two ways namely the organisms under ordinary conditions have low invasive power and the vast majority of persons have natural or acquired resistance In confirmation of the first postulate most strains in inter-epidemic periods belong to Group II or are rough and untypable Evidence of the truth of the second postulate is demonstrated by the presence of bactericidins and negative skin reactions in the vast majority of normal persons

Immunity—One attack of meningitis apparently *confers immunity* against reinfection and second attacks are rarely observed Following recovery from meningococcus meningitis, *bactericidins opsonins* and *agglutinins* may be demonstrable in the patient s serum Since they tend to disappear after a short time resistance is probably a matter of tissue rather than humoral immunity

The relatively low attack rate among persons exposed during an epidemic of meningococcus meningitis suggests that the majority of people have a natural immunity against this organism and indeed considerable bactericidal activity can be demonstrated in the blood of normal persons Epidemiological studies have revealed that the carrier rates of meningococci in the throats of healthy persons may be quite high at times This suggests that the majority of persons develop active immunity as a result of the carrier states of subclinical infection In support of this view is the fact that a high proportion of adults give negative skin reactions indicating immunity to the intradermal injection of Ferry s exotoxin In World War I the attack rates for meningococcus meningitis were much lower among men who came from large cities than among those from rural areas suggesting that immunity as the result of contact or subclinical infection had occurred among the former group

Pathogenesis of Meningococcal Infection—The portal of entry of the meningococcus is the *nasopharynx* From here invasive strains reach the blood stream directly or through the lymphatics Meningococci have been demonstrated in blood cultures in from 25 to 80 per cent of cases depending upon the adequacy of cultural methods It is probable that meningococcemia almost always precedes meningitis In most cases the bacteremia is transient so that blood cultures taken at the height of the meningitis are often sterile

It may be well to state at this point that most students of meningitis believe there is

in a chair and if this can be accomplished without excessive fatigue or tachycardia a trip is made to the bathroom for defecation If all goes well the child may then be given permission to walk about the room Later he is permitted the run of the house and finally an excursion is made out of doors on a fine day

These progressive and successive steps are checked by frequent pulse countings and temperature records If there is any significant disturbance progress is delayed until the variations level off

Preventive Treatment —There is every likelihood that an exacerbation will occur shortly following recovery from any acute rheumatic attack In consequence preventive measures are instituted as soon as convalescence has gotten well under way

Perhaps the most important single prophylactic measure is avoidance of contact with the beta hemolytic streptococcus To that end the child is isolated from those with respiratory disease Should the afflicted youngster develop a respiratory infection he is put back to bed and kept in bed until all of the specifications previously stated are again met

Since exacerbations of respiratory disease and rheumatic fever occur in spring and fall it is often wise to put the child to bed for a few weeks at each of these periods of the year

Sanitarium Treatment —From the medical standpoint alone there is no doubt that hospitalization or sanitarium care is preferable for the welfare of the rheumatic child Only emotional ties prevent most parents from seeking admission to the better equipped institutions

Climatotherapy —Climatotherapy is of proven prophylactic value in the management of the rheumatic child Hemolytic streptococcal infection is rare in semi tropical areas and desert states such as Arizona or New Mexico and exacerbations as the result of invasion by this organism are less likely to occur This has been best demonstrated by the transportation of a group of rheumatic children from northeastern United States to Porto Rico In the latter climate they remained free from new attacks of the disease but upon their return to the original habitat they again suffered frequent exacerbations

Enthusiasm for the prophylactic value of climatotherapy should not lead parents to believe that any great miracle is to be anticipated as a result of the geographical shift Climate has no curative possibility Damaged heart valves cannot be made new and the myocardium cannot be reconditioned

In private practice in contrast to institutional work it is necessary to weigh the possible benefits of a climatic change against the social economic and emotional factors that inevitably arise The child who leaves a comfortable well-established home to live under less favorable circumstances in a desert or a semi tropical climate may actually suffer from the transplantation

Prophylactic Chemotherapy —The prevention of recurrence in rheumatic fever may be accomplished by the judicious combination of prophylactic doses of salicylate and sulfonamide The first of these is utilized to prevent a recurrence of rheumatic fever following an acute streptococcic infection the sulfonamides are employed in the effort to prevent hemolytic streptococcus infection The combination of these agencies may be at

generalized eruption as the only distinctive feature *Fever enlargement of the spleen* and *leukocytosis* are usually present as in other infectious states

Eruption—A distinctive eruption occurs in from 10 to 20 per cent of patients afflicted with chronic meningococcemia the frequency varying in different epidemics The characteristic eruption is essentially a *capillary hemorrhage in the skin and mucous membranes* The spots vary in size from pinpoint lesions to irregular areas of 0.5 cm in diameter They are dusky red and do not fade on pressure Sometimes the rash is frankly purpuric especially in the more fulminating cases More often however the eruption is maculopapular resembling the rose spots of typhoid fever except that the individual lesion is larger and the rash is more abundant The



Fig 23—Purpuric rash of meningococcic meningitis

eruption is generally distributed over the body most particularly on the shoulders back abdomen and thighs In rare instances the spots are larger and elevated resembling *erythema nodosum*

Diagnosis—The diagnosis of chronic meningococcemia is suspected in the presence of an epidemic when the patient complains of generalized malaise and a rash is observed or described See *Differential Diagnosis of Generalized Rashes in Eruptive Fevers* (p 172)

Course—The course of chronic meningococcemia is variable Spontaneous recoveries and cures resulting from nonspecific protein therapy have been recorded In many of the untreated patients a meningitis is a terminal event unless specific therapy is vigorously instituted

Courtesy of Eli Lilly & Co

problem of surgical risk involves consideration of the effect of the operative procedure upon the infectious state and the effect of the infectious state upon the operative risk

One of the most important complications of rheumatic fever is subacute bacterial endocarditis resulting from streptococcemia Organisms may be introduced after the extraction of a tooth after tonsillectomy or following an abdominal procedure such as an appendectomy As a result surgical procedures are limited to *those of necessity* and should be preceded and followed by *prophylactic chemotherapy* using the sulfonamides or pen icillin (p 106)

When surgical procedures of necessity are performed on rheumatic chil dren it is surprising to see how well they tolerate the technical manipula tion

Marriage and Pregnancy—The practitioner is often asked to consider the advisability of marriage and pregnancy in rheumatic patients Though his advice is seldom taken he should attempt to postpone marriage par ticularly for the female patient until there has been a period of at least five years of quiescence If it is possible and permissible to do so conver sations should be held jointly with the afflicted patient and prospective marital partner It is only fair for the latter to know the risk that is being assumed and the heavy burden that almost inevitably impends

Despite these ominous warnings it is often remarkable to observe the longevity of patients with rheumatic valvulitis of moderate degree With modern methods of obstetrical anesthesia rheumatic women stand child birth amazingly well

THE PNEUMOCOCCUS

The pneumococcus is responsible for 95 per cent of all cases of lobar pneumonia as well as for occasional instances of pharyngitis sinusitis otitis media peritonitis meningitis and endocarditis

Bacteriology—Pneumococci are oval organisms occurring most characteristically in pairs When freshly isolated from human or animal infections they are encapsulated both mem bers of the pair of cocci being enclosed in a single capsule They are gram positive and non motile in fresh young cultures and do not form spores In smears pneumococci are generally quite distinctive but when they occur in chains they may be indistinguishable from strep tococci

Pneumococci are fastidious in their growth requirements and their successful cultivation generally demands *enriched* media Buffered meat infusion broth containing added dextrose may be sufficient for growth but better results are obtained when 2 per cent horse human or rabbit blood is added *Blood agar plates* are widely used since the appearance of colonies is most characteristic on this medium The organisms grow best at 37 C and are usually *aerobic* Occasionally a newly isolated strain grows better under reduced oxygen and in creased carbon dioxide tension but such strains are quickly adapted to aerobic growth In blood broth growth is evident in eight to twelve hours as a uniform even turbidity

On the surface of blood agar plates pneumococci develop as small round colonies with a flat surface and a raised edge somewhat resembling a checker They produce green dis coloration of the blood about the colony due to the conversion of hemoglobin to methemo globin In this characteristic they resemble the alpha or green streptococci and since pneu mococci often grow in chains some difficulty may be experienced in distinguishing between the two species Fortunately pneumococci exhibit two fairly constant and distinctive bio chemical reactions in that they regularly ferment inulin and are autolyzed by ox bile or bile salts

increases and smears reveal an early mononucleosis and a later polymorphonucleosis With increase in the leukocyte count the fluid becomes cloudy and later turbid and organisms are demonstrable both within and without the confines of the white cells A dry tap particularly in infancy suggests subarachnoid block and calls for a tap higher up preferably at the cisterna or the lateral angle of the anterior fontanelle (p 3783)

When intrathecal serum therapy was practiced interpretation of the *gross appearance of the cerebrospinal fluid was made more difficult* through the development of increased turbidity due to an aseptic meningeal reaction The treatment response could be differentiated from recrudescence or relapse by the clinical improvement of the patient and disappearance of demonstrable organisms despite increase in the leukocyte count Both penicillin and sulfonamides cause irritative meningitis neither however *to the degree that the inflammatory reaction is* evoked by serum

Differential Diagnosis —Meningococcal meningitis requires differentiation from the *nonsuppurative encephalomyelomeningitides* and from other forms of *purulent meningococcal reactions* In any instance observation of the cerebrospinal fluid is essential The clinician need have no hesitancy in performing or ordering the lumbar tap

Resemblance of meningococcal infection to the nonsuppurative meningitides is observed in mild and fulminating invasions In the presence of an epidemic epidemiologists increasingly recognize mild and carrier states in which the only findings may be soreness of the throat pharyngitis rhinitis tonsillitis or a conjunctivitis in which the organisms are clearly recognized in the purulent discharge These patients may have mild headache and some slight stiffness of the neck neither of which manifestations would be of sufficient degree to arouse suspicion under normal circumstances The diagnosis of meningeal infection is established only by smears from local inflammatory sites and the cerebrospinal fluid at most contains a slight increase in globulin and perhaps a mild monocytosis or polymorphonucleosis as in nonsuppurative disturbances of the coverings of brain and cord (p 442)

At the other extremes patients with acute and fulminating meningococcemia but without metastatic localization in the meninges also may exhibit a relatively normal cerebrospinal fluid Under these circumstance the clinical syndrome again resembles nonsuppurative encephalomyelomeningitis (p 442) except that the presence of bacteremia is readily established and the purpuric eruption points clearly to invasiveness by the gram negative organisms which can usually be demonstrated by direct blood smears taken from the more intense cutaneous lesions

The differential diagnosis of the varieties of purulent cerebrospinal meningitis is more than an academic discipline since in many instances surgical intervention is required in contrast to the condition that prevails in meningococcal invasion The diagnosis of the bacterial incitant of a *purulent meningitis is established conclusively in the laboratory* The presence of a gram positive coccus whether *staphylococcal* or *streptococcal* strongly suggests a focus in the nose accessory nasal sinuses middle ear mastoid process or brain tissue proper Septic meningitis also may be caused by compounded fractures of the skull and skin infections in areas drained by the facial veins In almost all of these examples antibiotic

nostic sera generally available. Cross reactions among types of pneumococci are noted occasionally, particularly between Types II and V and Types III and VIII. With modern high titer typing sera such cross reactions are rarely troublesome.

Diagnosis of Pneumococcal Infection.—The *Neufeld method* of typing pneumococci has displaced all other routine diagnostic methods. It is rapid and simple and with experience gives reliable and clearcut results. It requires a set of diagnostic typing sera which is commercially available for the commoner varieties. Many states as essential features of pneumonia-control programs have set up pneumococcus typing laboratories to which sputa and other materials may be sent for rapid diagnosis by the Neufeld method.

Pneumococci can be typed directly from sputum, spinal fluid, pus and other tissue fluids and from throat or blood cultures after preliminary incubation. For the successful typing of sputum it is essential that the specimen be coughed up from the lungs. When a satisfactory specimen has been obtained a small drop is placed on a coverslip and mixed with typing serum. A drop of methylene blue is added and the preparation is inverted on a glass slide and examined under the oil immersion lens of the microscope. In these preparations the pneumococcal bodies stain dark blue and well-defined capsules are generally seen. These may be quite large (especially Types III and VIII) and must be differentiated carefully from the true swollen capsule which characterizes the positive "*quellung*" reaction that results when pneumococci are mixed with homologous type specific antiserum. In the latter case the capsule becomes greatly swollen in size and assumes an opaque or ground glass appearance outlined by a definite clearcut border. The quellung usually appears within a few minutes but may take as long as half an hour to develop.

If organisms are not seen in the preparation it is obviously impossible to do a direct typing and *mouse inoculation* of the sputum is then necessary. Failure of quellung to occur with any of the specific sera may be due to excessive concentration of soluble specific substance in the sputum and dilution with saline or broth may allow the expected reaction to occur.

Typing of Sputum.—In practice Neufeld typing is facilitated by the use of 5 to 6 pools containing mixtures of type specific sera. These pools are commonly made up as follows:

A—Types I, II and VII
B—Types III, IV, V, VI and VIII
C—Types IX, XII, XIV, XV and XVII
D—Types X, XI, XIII, XX, XXII, XXIV
E—Types XVI, XVIII, XIX, XXI, XXVIII
F—Types XXIII, XXV, XXVII, XXIX, XXXI, XXXII

A drop of sputum is mixed with one or two drops of serum from each pool. Then the sputum is tested with each of the typing sera contained in the pool in which quellung was observed (Fig. 92). If too few organisms are present in the sputum for successful typing a portion of washed sputum may be inoculated into blood broth, incubated for four to six hours and then examined by the Neufeld method. If possible, however, it is preferable to inject 1.0 cc of the sputum intraperitoneally into a mouse. This animal serves as an excellent incubator for the pneumococcus which tends to outgrow contaminating organisms. In six to eight hours there may be an almost pure culture of pneumococci in the peritoneal exudate. This is aspirated with a capillary pipette and Neufeld typing is done. If rapidity of diagnosis is not essential one can wait for twelve to eighteen hours until the mouse dies of septicemia and recover the organisms from the peritoneum or the heart's blood.

In children in whom it is often impossible to obtain sputum, throat cultures should be obtained and incubated for four hours in blood broth. At the end of that time an attempt may be made to perform Neufeld typing on the broth culture. If the results are still negative 1.0 cc may be injected intraperitoneally into a mouse.

Sputum, pus, spinal fluid and other materials are streaked on the surface of a blood agar plate at the time the specimen is obtained regardless of the results of the Neufeld test. This is done to make sure that other organisms of possible etiologic significance (staphylococci and hemolytic streptococci) are not overlooked. The added precaution of making a carbol fuchsin stain occasionally reveals the unexpected presence of tubercle bacilli (p. 52).

An examination of stained smears of the sputum noting the number of organisms, the amount of phagocytosis and the presence or absence of clumping of the pneumococci is

There is little doubt that serum therapy should not be attempted until the less cumbersome and less toxic sulfonamide preparations and penicillin have been given a thorough trial Serum therapy may then be given as a substitute or in conjunction with the anti infective agents particularly in young infants and debilitated adults who fail to respond or in the presence of moderate to severe toxemia

Anti infective Agents—All types of meningococcemia and meningococcic cerebrospinal meningitis respond to the sulfonamides and penicillin Some technical difficulties are encountered with these modalities in that there is difficulty in traversing the pia arachnoid barrier and intrathecal instillation is required

If the patient is to be treated by oral dosage, *sulfadiazine* is the preparation of choice Under no circumstance should sulfathiazole be used since the pia arachnoid is least permeable to this preparation For the adult of average size the initial dose should be no less than 6 and preferably 8 gm (90 to 120 grains) in conjunction with 1 teaspoonful of bicarbonate of soda and at least 1 glass of water Subsequent doses may be 1 gm (15 grains) with which the bicarbonate and water are given at three or four hour intervals day and night With adequate sulfonamide therapy the mortality of the disease varies between 2 and 10 per cent

Because of the severity of meningococcal infection most experienced clinicians favor an initial *intravenous dose* of at least 5 gm of *sodium sulfadiazine* which may be administered in 100 cc of 5 per cent solution or 20 cc of 25 per cent solution The latter must be given by extremely slow injection using a 20 cc syringe and a 26 gauge hypodermic needle Subsequent doses may be given by the oral route or half of the initial dose may be given intravenously at six or eight hour intervals

As in the instance of staphylococcic and streptococcic infections there is good reason to believe that *penicillin* is superior to sulfadiazine in the treatment of coccal invasion The dose of penicillin may be given *intramuscularly* or *intravenously* The initial amount should be no less than 100 000 units and preferably 250 000 to 500 000 units subsequent doses given at three or four hour intervals may vary between 50 000 and 100 000 units The superiority of penicillin is due to the almost complete absence of toxic effects and its potent effects on the invading organism In overwhelming protracted or seemingly resistant infection especially in the weakened the aged and the very young high concentrations of penicillin effected by massive daily dosages of 500 000 to 1 000 00 units or by the production of blockade (p 109) are worthy of earnest consideration

Like the sulfonamides penicillin does not penetrate well into the cerebrospinal fluid and it is good judgment to perform *lumbar puncture* remove as much spinal fluid as possible and replace it with 1 or 2 cc less of a preparation of penicillin containing 50 000 units in physiologic saline solution *Subarachnoid* or *intracisternal injections* may be practiced once or twice daily until the condition is under complete control Should there be a complete block particularly in the infant whose fontanelle has not yet closed the *intraventricular instillation* is safe and practical

Combination Therapy—There is no reason why sulfonamides and penicillin cannot be combined in the treatment of meningococcemia and men

consisting of erythema at the site of injection A negative test indicates lack of type specific antibodies The Francis test was intended as a means of controlling the amount of therapeutic antipneumococcus serum required for the treatment of an individual patient Unfortunately the test is not nearly as specific as it was originally believed since false positive and false negative reactions occur with considerable frequency

Immunity—Recovery from pneumococcal infection confers little or no durable immunity against reinfection Humoral antibodies are rarely present in high titer and indeed may be entirely absent in patients who recover from pneumococcal infection by spontaneous crisis Sulfonamide drugs do not interfere with the development of antibodies either favorably or adversely

Humoral antibodies rapidly disappear during convalescence and such tissue immunity as is presumably engendered by recovery from an attack of pneumonia is soon lost Second attacks of pneumonia are common even with the same type of pneumococcus and may occur within a few weeks after recovery from the first attack A considerable proportion of patients with pneumonia give a history of having had a previous attack Second attacks are in general similar to the first attacks in severity and the number of lobes involved The lobes originally involved apparently do not develop any local immunity but neither is there greater local susceptibility unless the site involved is affected with obvious chronic disease such as bronchiectasis

Epidemiology—The pneumococcus is a natural parasite of man Under usual conditions it does not long survive outside of human tissues The organism is quite susceptible to the lethal effects of sunlight and will die within an hour when exposed to the direct rays of the sun. In a dark moist environment outside of the human body however it may survive for as long as a week. The organism is extremely prevalent in the human nasopharynx and at least 50 per cent of normal persons at one time or another harbor pneumococci The great majority of individuals carry pneumococci of the higher types and relatively few carry the more virulent common types (I II V VII and VIII)

"Healthy Carriers"—The incidence of normal healthy carriers of Type I pneumococci is about 0.5 per cent of Type II 1 0 per cent and of Type III about 10 per cent For this reason pulmonary infections with Types I and II are more likely to be "exogenous" while infection with Type III may be "autogenous" Patients convalescent from pneumococcal infection may continue to carry the organisms for weeks or even months

Transmission—Pneumococcal infection is most often transmitted from the respiratory tract of one person to another Transmission may be direct as a result of coughing sneezing and the like or indirect by the air borne transmission of dried sputum or droplet nuclei Since pneumococcal infections are transmitted through the respiratory tract, they occur most commonly in winter and early spring The peak incidence in this country is in early March

Pneumococcal infection is generally sporadic although occasionally epidemics of Types I II and V pneumococcal pneumonia occur A high proportion of family contacts of a patient with pneumonia harbor the homologous pneumococcus While it is generally considered that the organism is transmitted from the patient to his immediate contacts there is increasing evidence that the transmission actually may be in the opposite direction For example one member of a family becomes a carrier The member of the family whose daily business brings him into association with crowds of coughing sneezing individuals in office street car bus and restaurant is the one most likely to become infected He then transmits the organism to the family group some of whom remain healthy carriers while others develop minor respiratory infections such as otitis media and lobar pneumonia A bacteriological diagnosis is made ordinarily only on the patient with pneumonia and not on the other members of the family Hence the impression is gained that pneumonia is an isolated sporadic infection whereas in fact it may be the visible manifestation of a small family epidemic There is some evidence that this situation may occur even in the community at large

Obviously factors other than the presence of a potentially virulent pneumococcus determine whether a "carrier state" (p 147) or a clinical infection will result As mentioned previously most persons have a considerable degree of natural resistance to pneumococcal infection Some additional factor or factors which lower resistance are present in those patients who develop clinically apparent diseases Among such factors are acute minor respiratory infections exposure to temperature variations chilling wetting fatigue and acute or chronic alcoholism

apes have failed The organism is lethal for small laboratory animals when large doses are *injected intraperitoneally* but *this action is ascribed to toxicity as there is little evidence* that the organisms actually proliferate in animal tissue

Subgroups—By agglutinin absorption technics it is possible to demonstrate the existence of a number of strains of gonococci However much antigenic overlapping exists among strains and it is not possible to speak of distinct serological groups or types Organisms isolated from acute lesions differ antigenically from old laboratory cultures and from strains isolated from patients with chronic gonorrhea Although it was thought previously that the cocci isolated from children with vulvovaginitis differ from those producing acute urethritis in adults this view is no longer accepted

By chemical fractionation gonococci have been found to contain *polysaccharides* and *nucleoprotein fractions* similar to those present in meningococci Considerable cross agglutination occurs between the two organisms and the serum of patients with meningococcus infection may give a positive complement fixation reaction with gonococcus antigen It is almost certain that type specific substances are present in various strains of gonococci and that a classification based on such substances will eventually be developed

Toxin Production—Gonococci liberate *endotoxins* when grown in fluid medium Some bacteriologists state that *exotoxins* are formed also but final evidence for this has not been presented

Immunity—It is unlikely that human beings have any natural immunity to the gonococcus although some types of epithelial surfaces are more resistant to infection to others Most normal individuals have but little natural bactericidal activity in the blood In cases of gonorrhea serum *bactericidins* are temporarily increased but only to an insignificant degree and agglutinins are not produced regularly in high titer Attempts to develop a skin test which would indicate immunity to the gonococcus have given results that are erratic and unreliable

Normal phagocytes ingest gonococci but they do not commonly kill them *Acquired immunity* as a result of infection is never very potent and *reinfection is a common experience* Gonococcus vaccines are ineffective both in the prevention and in the treatment of the disease

Transmission—*Conjunctivitis neonatorum* develops in the newborn during passage through the infected tissues of the mother in parturition The adult conjunctival mucosa is undoubtedly more resistant than the infantile since gonorrheal conjunctivitis in adults is rare although the opportunity for the transmission of infection from the urethra to the eyes is very great

Vulvovaginitis of children occurs most often in hospital wards or institutions as the result of extragenital infection the organism being spread by contaminated linen and bed clothes towels and rectal thermometers The gonococcus is best able to infect mucous membranes lined by single-layered columnar epithelium hence it attacks the vaginal mucosa of children whereas the vagina of adult females is quite resistant This observation is the basis for treatment with *estrogenic substances* intended to produce in the child's vagina a stratified squamous epithelium in which the gonococcus cannot maintain itself

In adults the gonococcus is almost always transmitted by direct *sexual contact* from the mucous membranes of one genital tract to another

Clinical Manifestations

For the most part gonococcal infections consist of local inflammatory processes and complications that arise by extension Only under unusual circumstances is a bacteremia produced with its attendant *metastatic* sequels

Local Inflammatory Processes—In the male gonorrheal invasion produces *urethritis*, with its complications in the remainder of the genital tract These are more fully described in the section on the male reproductive system (p 2393)

In the female the gonorrheal implants may be *urethral* or *vulvovaginal* The complications by extension are of a graver nature since the fallopian tubes the ovaries and their pelvic peritoneum occupy an intra abdominal

comparison is possible *penicillin* is the preparation of choice due to its powerful organotropism and its absence of toxicity The local instillation of the *sulfonamides* may be highly effectual but local and systemic toxicologic phenomena may be induced *tyrothricin* exposes to the hazard of a hemolytic reaction and high concentrations may produce corneal clouding For instillation into the conjunctival sac a penicillin solution may be made up containing 1000 to 5000 units per cc satisfactory results have also been obtained with an ointment of 1000 to 5000 units of penicillin in 1 cc of petroleum jelly These preparations do not harm the cornea but are powerfully pneumococcidal

Serum Therapy —*Antipneumococcal serums* (U S P) have been obtained by immunization of horses or rabbits with one of the specific types of pneumococcus The official preparations include antipneumococcic horse serums for all types except IV VII XIV XXVI and XXX The official antipneumococcic rabbit serums include those for Types I II III V VII VIII and XIV

In the era that preceded the amazing accomplishments of anti infective therapy the benefit of serum treatment was regarded as a major triumph in medicine despite the fact that the technic was cumbersome It involved the collection of sputum typing testing for sensitivity and finally the intravenous injection of the product after definitive identification of the type specific invading organism Under best circumstances a fairly large proportion of the patients developed serum sickness and other untoward manifestations

The entire procedure involved far too many difficulties had excessive risk for routine use in private practice and was almost wholly limited to institutional work The conscientious practitioner was often disquieted by the thought that his patient with lobar pneumonia could not be the recipient of optimum treatment Often he was tempted to suggest hospitalization for more expert management

The introduction of the anti infective agents has happily resolved the practitioner s dilemma It is quite within the realm of possibility that serum therapy in lobar pneumonia may soon be relegated to the shelves of medical history Certainly its present role in patient management can only be that of a third substitute after trials with penicillin and sulfonamide If serum is to be used at all the rabbit product is to be preferred since it possesses several distinct advantages over horse serum The antibodies of rabbit serum are of smaller molecular size and probably penetrate the tissues more readily the product is richer in protective antibodies so that the concentration of the antibacterial substance is greater anaphylactic phenomena are less frequent and milder and sensitization is less likely to occur Monovalent type specific sera in vials containing 50 000 units are purchasable for Types I II III IV V VI VII VIII IX X XI XII XIII XIV XV XVI XVII XVIII XIX XX XXI XXII XXIII XXIV XXV XXVII XXVIII XXIX XXXI and XXXII

Anti infective Agents —The *sulfonamides* and *penicillin* possess remarkable therapeutic qualities in the treatment of pneumococcal infection The practitioner has his choice of the use of one or other or both of these remedies with almost certain assurance of a specific therapeutic result unless host defenses are extraordinarily feeble or a resistant strain of organ

ritis (p 2336) *of non venereal origin, an occasional coccal organism appears* to decolorize by the Gram method The confusion is increased when the bacterium occupies a position on rather than within a leukocyte To assume that this is a gram negative intracellular diplococcus may be a bacteriological error of only minor importance but the sociological implications are great The patient may suffer an unjustified stigma or he on his part may place an undeserved onus on his consort or sexual contact

To avoid unfortunate errors the practitioner should use meticulous care in the preparation and examination of smears Despite the technical difficulties he should attempt to supplement the morphological examination by cultural methods

Culture —There can be no question as to the superiority of cultures over smears in the diagnosis of gonococcal infection In cervicitis and other forms of chronic gonorrhea in females positive smears are found in no more than half of the cases In males the proportion of positive smears is high but never approaches 100 per cent On the other hand, gonococci can be isolated *by cultural methods from 90 per cent of acute cases of gonorrhea* in males and in 75 per cent or more of acute cases in females In chronic gonorrhea the results are less consistent but are still far superior to those obtained by the examination of smears alone When the *sulfonamide drugs* are administered it is not uncommon for the smear to become negative while the culture continues to be positive Reliance on the results of smears alone leads to unwarranted optimism and a premature verdict of cure

For cultural investigation a sterile swab is impregnated with suspected discharge or material and placed in a tube containing 1 0 cc of sterile broth or semi solid dextrose starch agar (Difco) The tube is immediately incubated at 36° C or placed in the refrigerator but should not be kept at room temperature since this allows the overgrowth of contaminating organisms and prevents the growth of gonococci In the incubator the gonococcus and all other contaminants have an equal chance to grow in the refrigerator all are equally inhibited From the incubator or refrigerator the tubes are transferred to the laboratory for culture Many media have been devised for the growth of gonococci but *chocolate agar* has stood the test of time This preparation is made by adding 10 per cent of citrated or defibrinated human horse or rabbit blood to melted meat infusion agar at a temperature of 80° C A commercial dehydrated medium (Difco) is available for use in smaller laboratories where gonococci are cultured only occasionally

The inoculated plates are best incubated at 36° C and in an atmosphere containing 5 to 10 per cent carbon dioxide This may be obtained by the use of a gas apparatus but the simple candle jar serves equally well Moisture is essential for growth and this is provided by placing a layer of wet cotton in the bottom of the candle jar Growth is evident in twenty four hours but occasionally forty eight hours incubation may be required

Gonococcus colonies are flat transparent from 1 to 3 mm in diameter and have somewhat irregular undulated margins Young colonies of streptococci and diphtheroids may resemble gonococci Of great help in differentiating the Neisseriae from most other organisms is the fact that they contain an oxidase which in the presence of dimethyl paraphenylene

The Prevention of Pneumococcal Infection

Although laboratory animals can be successfully immunized against pneumococcal infection there is as yet no clear evidence that this procedure can be employed successfully in man Since an attack of pneumonia confers little or no immunity (p 76) artificial immunization can hardly hope to do more than an actual attack of the disease

Vaccine—There have been numerous clinical trials of attempted immunization using *polyvalent pneumococcal vaccines* that included all of the common types (p 77) The largest and most continuous study has come from South Africa where for many years the morbidity from pneumonia among native miners has been extremely high The experience of the South African workers may be summarized by the statement that there is little conclusive evidence that vaccines have any notable effects in reducing the incidence or mortality of pneumonia

Polysaccharide—In the United States an attempt has been made to produce mass immunization by the intradermal injection of type specific polysaccharides (p 588) Although a large number of young adults have been treated it is difficult to attest the value of the procedure since the incidence of pneumonia has been quite low in the control group

authorities are in agreement that the instillation of 1 or 2 per cent *silver nitrate* as demanded by law in most states constitutes the most effectual method Solutions of *silver proteinate* are less irritating but also less successful Instillations of penicillin should prove nonirritating and effectual

Venereal Prophylaxis by Local Chemotherapy —The approved methods of venereal prophylaxis as adopted by the Army and Navy are described elsewhere (p 3122) Correctly used these methods are of undoubted value in the male Practically their successful application is limited by the intelligence cooperation and sobriety of the exposed individual Certainly they have little value in the female

Venereal Prophylaxis by Systemic Use of the Anti infective Agents—The prophylaxis of gonorrheal urethritis is successfully accomplished by the systemic use of the sulfonamides In army encampments the administration of 2 gm of *sulfadiazine* to men with an overnight pass and an additional 2 gm on the day following their return resulted in a fall of the gonorrhea rate from 171 per thousand to 8 per thousand Simultaneously the rate of *chancroid* infections fell from 52 to 6 per thousand Prophylactic chemotherapy with the sulfonamides holds great promise since it does not require instrumentation and is as efficacious in the female as in the male There is concurrent protection against chancroid but none against syphilis

Whereas the efficacy of *penicillin* as a prophylactic against gonorrhea has not yet been thoroughly tested it is worthy of the consideration of the private practitioner who may assume that the patient who has been exposed to gonorrhea has an excellent chance of having been exposed simultaneously to syphilis Since penicillin unlike the sulfonamides exerts its potent action against the *Treponema pallidum* as well as the gonococcus an intramuscular injection of adequate doses of this remedy may successfully prevent both venereal infections The practitioner is warned against insufficient penicillin dosage in suspected combined infection Small amounts of the antibiotic sufficient to prevent gonorrhea may merely mask a syphilis and even sensitize the invader against the therapeutic agent If systemic penicillin is used for venereal prophylaxis it would seem ill advised to start treatment unless at least 1 000 000 units could be injected using 50 000 units every three hours

Gonococcus Vaccine —Gonococcal vaccine is useless its prophylactic administration should be abandoned

CURATIVE TREATMENT

In the era that preceded anti infective agents the treatment of gonococcal infections was confused and unsatisfactory A host of preparations for local and systemic use was available Each modality had its enthusiastic proponent who claimed brilliant results which the humble and more objective practitioner could not repeat With the advent of the truly specific routine it has become apparent that much of the enthusiasm for the previous forms of therapy was unfounded and that more harm than benefit followed overzealous instrumentation

Anti infective Agents —For the oral treatment of gonococcal infection the practitioner may use *sulfadiazine sulfamerazine* or *sulfathiazole* The initial dose need be no higher than 4 gm (60 grains) and subsequent doses

There is considerable variation in their size and shape With appropriate technic many freshly isolated strains can be shown to be encapsulated They are non motile and non sporeforming and readily d sintegrate in spinal fluid which is permitted to stand about at room temperature for any length of time

Meningococci are exacting in their cultural requirements and will not grow on plain agar The most suitable medium is infusion agar to which blood, serum or ascitic fluid has been added Five or 10 per cent blood agar plates such as are used for the routine isolation of pneumococci and hemolytic streptococci are also suitable for the cultivation of meningococcus Chocolate agar made by heating blood to 80 C before mixing with agar is also suitable A simplified and inexpensive medium consists of infusion agar to which casein hydrolysate and starch are added.

Meningococci grow best at 37 C poorly if at all at room temperature Concentrat ons of 5 per cent CO in the atmosphere readily obtained in the ordinary candle jar enhance their growth The colonies of meningococci are quite characteristic on the surface of blood agar plates After twenty four hours incubation they are 2 to 3 mm in diameter transparent circular and hemispherical in shape Under obl que illumination they have a grayish semi-opaque appearance After prolonged laboratory cultivation rough variants develop which are smaller and have a coarser crenated surface Meningococci produce acid but not gas from glucose and maltose and do not ferment lactose or sucrose This reaction is of differential value in separating meningococci from gonococci and other Neisseriae

Classificat on—By serological morphological and chemical methods various attempts have been made to recognize *antigenic differences* among strains of meningococci

AGGLUTININ ABSORPTION—The great prevalence of epidemic meningitis during World War I resulted in the recognition of Types I II III and IV by a glutinin absorption tech nics This classification has since undergone modification through the findings that Types I and III are closely related if not identical These types are not included in the newer classification of meningococci as Group I Type II apparently consists of many heterologous strains wh ch have enough in common to be classified at present as Group II but the posi tion of the old Type IV is obscure Organisms apparently related to this type were isolated in an epidemic in Chicago a number of years ago but have not since been found Among the many heterogenous strains included in Group II ther are a number which are closely related to one another and these are grouped as II A

SMOOTH AND ROUGH STRAINS—Both "*smooth* and *rough* strains of meningococci exist Organ sms freshly isolated from the spinal fluid of patients with meningitis are generally smooth On prolonged laboratory cultivation rough" variants develop and from the throats of many normal meningococcus carriers rough untypable strains have been isolated

Morphological studies reveal capsules on meningococci and it is possible to carry out a *quellung* reaction (p 201) in spinal fluids or in fresh culture using group pecifc antisera Only smooth mouse virulent organisms of Groups I and II A have capsules The group specific antigen which is responsible for capsule swelling can also be demonstrated in several other ways When meningococci are planted on the surface of an agar plate to which 5 per cent group specific antiserum has been added a precipitate or "halo forms in the med um about the colony due to the combination of group specific polysaccharide and antiserum The layering of supernatant spinal fluid obtained f om a patient with meningitis over a specific antiserum produces a positive *precipitin reaction* if the organism and the s rum are homologous

CHEMICAL FRACTIONS—The attempt to group meningococci serologically has led to the recogn t on of three chemical fract ons One is a *carbohyd ate* present in all strains of men ingococci as well as in other Neisseriae and probably similar to the "C substance obtained from pneumococc Another fraction is *protein* in nature and is likewise common to the other Neisseriae Both of these substances are no doubt part of the somatic structure of all Neisseriae A third fraction a *polysaccharide* has been isolated from Group I meni gococci It is pre ent on the surface and is related to capsule swelling halo" formation and mouse virulence Th s f an analogous substance has not been isolated from Group II stra ns

All strains of meningococc are agglutinated by polyvalent antimeningococcal serum wh n incubated at 37 C However at 56 C agglutinat on does not occur unless the antiserum s monovalent and group specific

GROUPS—The great majority of epidemics of men ngococcus meningitis in the p t twenty five years have been caused by organisms belonging to *G oup I* and 90 per cent of all epid mic strains have been identified as members of this group Group I strains a e ant

forms of fever therapy have been introduced with striking success particularly in the chronic infections Whether the various forms of hyperpyrexia act by a direct lethal influence on the organism or by stimulation of tissue immunity is not known Hyperpyrexia may be achieved by mechanical agencies such as the *hypertherm* or by the injection of *nonspecific proteins* such as sterile boiled milk or intravenous typhoid vaccine

Systemic hyperpyrexia is of greatest value in chronic localized gonococcal infections such as arthritis, pelvic peritonitis and tubo-ovarian involvement Less frequently the method is successful in otherwise fatal gonococcal endocarditis Hyperpyrexia does not preclude the use of systemic chemotherapy Rather does the increased febrile reaction enhance the efficacy of the sulfonamides Hence combination methods of therapy are advisable

In addition to systemic hyperthermia *local heat* by use of the *Elliott machine* or by *diathermy* (p 3768) is widely and successfully used in the treatment of chronic pelvic inflammatory disease These technics are elsewhere described with their specific indications They carry less risk than systemic hyperpyrexia and can be employed by the practitioner who does not necessarily need to institutionalize his patient

In the presence of persistent infection especially if associated with conjunctivitis and arthritis and without definitive bacteriologic findings Reiter s disease may be suspected (p 484)

Estrogen Therapy—The specific indication for the use of estrogenic preparations is vulvovaginitis in children The preparations can be given orally parenterally or by vaginal suppository (p 2515)

no clear evidence that the performance of lumbar puncture in the presence of bacteremia is likely to introduce organisms into the spinal fluid. Since clinical examination is not sufficient to rule out the presence of meningitis and it is a common experience to find extensive pathological involvement of the meninges without clinical signs lumbar puncture is the only way that the diagnosis can be made with certainty and that proper treatment can be instituted promptly

CLINICAL MANIFESTATIONS OF MENINGOCOCCAL INFECTION

The clinical manifestations of meningococcal invasion include acute *fulminating and chronic examples of meningococcemia and cerebrospinal* meningitis

ACUTE MENINGOCOCCEMIA

Acute meningococcemia in the pre meningitic phase is being recognized with increasing frequency. At one time considered a rare affliction it was recently recognized in 39 of a group of 112 patients with meningococcic infection. The remainder presented the clinical syndrome of a meningitis

Acute meningococcemia is almost invariably preceded by an upper respiratory infection. *Headache* is a complaint in each of the patients and the majority also suffer from *nausea*. The pathognomonic feature upon *which diagnosis is based particularly in the presence of an epidemic is the generalized eruption* which may be petechial purpuric macular or maculo papular many of the patients have a *herpes simplex* and approximately half complain of *joint pain* (Fig 93 p 212)

A positive diagnosis of meningococcemia is established by making a stained smear of blood obtained by superficial puncture from a meningococcic eruption which will reveal the organism in most instances. More definitive evidence is established from the positive *blood culture*. The absence of meningeal irritation is confirmed by the presence of *normal spinal fluid findings*

FULMINATING MENINGOCOCCEMIA (WATERHOUSE FRIDERICHSEN SYNDROME)

The Waterhouse Friderichsen syndrome is an acute fulminating meningococcemia *in which the patient dies before meningitis has had time to* develop. The manifestations which fortunately are rarely observed consist of an acute rapidly fatal affliction in which there are symptoms of associated shock and collapse explicable at autopsy by the presence of bilateral *adrenocortical hemorrhage and necrosis* (p 1271)

CHRONIC MENINGOCOCCEMIA

In *striking contrast to the Waterhouse Friderichsen syndrome chronic* meningococcemia may be a mild and insidious disease. The patient complains of relatively minor symptoms such as intermittent headache myalgia arthralgia or a fleeting eruption and notes a low grade fever and a certain amount of malaise. The *symptoms* are often of such *inconsequential degree* that the patient remains ambulatory and may even continue at work for several weeks despite the fact that there is every likelihood that an intermittent or even continuous bacteremia is present. The examination of the patient with chronic meningococcemia presents the

TABLE 21.—CHARACTERISTIC REACTIONS OF ENTERIC ORGANISMS

ORGANISM	MOTILITY	KRUMWIEDE	SUGAR FERMENTATIONS					INDOLE
			LACTOSE	DEXTROSE	MANNITOL	SUCROSE	XYLOSE	
Escherichia coli	+	AG	AG	AG	AG	AG or V	AG or V	+
Eberthella typhi	+	A	–	A	A	–	V	–
Salmonella typhi murium	+	AG	–	AG	AG	–	AG	–
Salmonella schottmuelleri	+	AG	–	AG	AG	–	AG	–
Shigella shiga	–	A	–	A	–	–	–	–
Shigella Newcastle	–	A	–	A slight gas	A	–	V	–
Shigella flexneri	–	A	–	A	A	A or V	–	±
Shigella sonnei	–	A	A (late—4 to 10 days)	A	A	A (late—4 to 10 days)	–	–

Krumwiede AG = acid + gas
A = acid butt

Sugar reactions AG = acid + gas
A = acid no gas
V = variable reactions

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Salmonella schottmuelleri	+	AG	–	AG	AG	–	AG	–
Shigella shiga	–	A	–	A	–	–	–	–
Shigella Newcastle	–	A	–	A slight gas	A	–	V	–
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CEREBROSPINAL MENINGOCOCCIC MENINGITIS

The astute recognition of the phase of acute meningococcemia and the prompt institution of effectual therapy have apparently diminished the incidence of meningococcic meningitis In the series of 112 patients to which reference was previously made only 80 had the clinical symptoms of the meningeal irritation In these cases in addition to the manifestations of the acute meningococcemia *chills* were noted in 50 per cent *stupor* in 44 per cent *cranial nerve involvement* in 10 per cent and *stiffness of the neck* in 99 per cent *Leukocytosis* was present in all cases and the spinal fluid findings were distinctly positive Organisms were present in the smear in 70 per cent and on culture in 81 per cent The fluid was grossly turbid and contained myriads of leukocytes many with intracellular gram negative organisms A positive blood culture was established in 40 per cent

Clinical Manifestations—In addition to the eruption and fever of acute meningococcemia the patient with metastatic purulent cerebrospinal meningitis exhibits localizing symptoms Usually he assumes the lateral decubitus with knees drawn up and head bent forward The mental state may vary between dulness and apathy to active delirium The principal complaints are bursting headache which is intensified by persistence of vomiting generalized body soreness and joint pains occasionally with swelling

Physical examination reveals retraction of the head stiffness of the neck and positive Kernig and Brudzinski signs The pulse may be relatively slow in proportion to the febrile elevation Often there is a tache cerebrale Pupillary dilatation and irregularities are seen in the more severe manifestations Strabismus is noted when there are oculomotor palsies By ophthalmoscopy fullness of retinal veins retinal edema hemorrhages and papilledema occasionally are noted Herpes of lips or face is a frequent and suggestive clinical clue In infancy the fontanelles bulge and intracranial complications are encountered more frequently

Course and Complications—In the eras that preceded antibiotic therapy the course of a cerebrospinal meningitis was punctuated by frequent complications and fatalities were experienced in almost half of the afflicted Toxic sequels were those of the acute meningococcemia (p 217) and the more rapidly overwhelming Waterhouse Friderichsen syndrome (p 211) Local metastatic complications included purulent conjunctivitis panophthalmitis otitis media pericarditis and arthritis Infants particularly were prone to develop *internal hydrocephalus* from subarachnoid block which usually occurred at the roof of the fourth ventricle With this distressing complication headache became unbearable the face appeared cyanosed the veins of the forehead distended ocular palsies developed and the child might succumb in coma or following convulsive episodes Non purulent complications of cerebrospinal fever included retention of urine bronchitis pneumonitis transitory blindness and permanent deafness

Diagnosis—The diagnosis of meningococcic cerebrospinal meningitis is established clearly by examination of the cerebrospinal fluid which can be obtained by lumbar puncture in the adult or additionally through the fontanelle in infancy In pure meningococcemia the cerebrospinal fluid may remain altogether normal but with the development of metastatic meningitis isolated organisms are demonstrable the amount of globulin

Pathology—The *portal of entry* of typhoid bacilli is the lymphoid tissue of the small intestine where the earliest lesions occur From there the abdominal lymph nodes draining the bowel are infected The bacilli multiply in the lymph nodes during the period of incubation and then by way of the thoracic duct reach the blood stream to initiate the period of systemic invasion Subsequent to the bacteremia the bacilli localize in the hematopoietic tissue particularly the reticulo-endothelial and lymphoid tissue of the intestinal wall ("Peyers patches) abdominal lymph nodes spleen liver and bone marrow

Cellular Reaction—Typhoid bacilli excite a characteristic and unique cellular reaction unlike the suppurative lesions produced by pyogenic cocci or the granuloma of syphilis and tuberculosis The predominant cell is the large macrophage of the reticulo-endothelial system which appears in the local lesions of the liver the stroma of the lymph nodes and the Peyers patches of the bowel



Fig 24—*A* Swollen Peyers patches in typhoid fever *B* Ulceration of Peyers patches in typhoid fever *

Intestinal Lesions (Peyer's Patches)—The intestinal lesions are most marked in the lower ileum in the region of the ileocecal valve although they may also involve other parts of the small intestine and the colon The *Peyer's Patches* (Fig 24) crowded with large mononuclear phagocytes enlarge in size until they project above the mucosal surface Towards the end of the period of systemic involvement and bacteremia these intestinal lesions become necrotic The overlying mucosa forms a slough which later separates and leaves a round or irregularly oval ulcer with its long axis in the long axis of the bowel These ulcers are usually quite superficial but at times may be deep enough to involve the muscular layers and reach the serosa accounting for the *hemorrhages* and *perforations* responsible for the majority of deaths In favorable cases the ulcers completely heal with the formation of little or no scar tissue

* MacCallum Textbook of Pathology

therapy requires supplementation with surgery if a successful result is to be obtained

In infancy purulent meningitis may result from invasion of *H influenzae* readily recognized in the cerebrospinal fluid as a short gram negative bacillus often encapsulated (p 285) The utility of anti H influenzae Type B rabbit serum in conjunction with the sulfonamides accentuates the importance of the differential bacterial diagnosis

Finally meningococcal meningitis must be separated from the *meningismus* that occurs in many acute infectious diseases Headache and some stiffness of the neck may be encountered in such diverse conditions as scarlet fever influenza typhus pneumonia mumps typhoid fever tonsillitis food poisoning tetanus rheumatic fever subarachnoid hemorrhage diabetic or uremic coma tetany cerebral abscess cerebral hemorrhage and cerebral thrombosis brucellosis and trichinosis Under these circumstances security dictates the necessity for performance of the lumbar puncture the presence of clear fluid establishes the integrity of the meninges at least for the moment

So far as the course of cerebrospinal meningitis is concerned the successful introduction of antibiotic therapy should render obsolete the distressing clinical pictures of the past With intensive therapy by systemic and intrathecal injection the clinician should observe prompt defervescence with amelioration of symptoms except under the most unusual circumstances of lack of host resistance overwhelming invasiveness or organism fastness

TREATMENT

The patient with meningococcal infection is treated according to the general principles established for each of the infectious diseases (p 43) Strict isolation is demanded and it is required to report the infection to the public health authorities For specific therapy the practitioner has at his disposal Meningococcus Antitoxin N N R Antimeningococcic Serum N N R the sulfonamides and penicillin

Serum Therapy—The brilliant accomplishments of anti infective agents make it quite apparent that serum upon which reliance was so heavily placed in earlier days is not and probably was not a particularly potent therapeutic agency So greatly has confidence been lost in immunotherapy that the Council on Pharmacy of the American Medical Association voted in 1944 to omit from N N R the antimeningococcic serum and meningococcus antitoxin Despite the almost certain wisdom of this decision it is our opinion that serum therapy should be kept available as a third choice in the rare instance in which sulfonamide and penicillin fail to produce their usual beneficial effects

Antimeningococcus Serum and Meningococcus Antitoxin—Serum therapy may be given by the intravenous intramuscular or intrathecal routes The method of choice is *intravenous injection* employing the usual safeguards that are required in all types of serum therapy The *intramuscular route* is useful only when it is technically difficult to make an intravenous injection as in infants and young children and *intrathecal injections* have been almost completely abandoned since there is general agreement that repeated lumbar puncture with the instillation of a foreign protein produces much more unfavorable reaction than specific therapeutic benefit

themselves such as roughness or smoothness and the presence of Vi antigen The low attack rate of common source epidemics indicates that infection is dependent as much on the state of host resistance as it is on the properties of the organisms

During the preliminary phase the patient complains of a vague deviation from normal well being He notes *lassitude malaise* and *headache* in practically all instances *Anorexia* is most common and at least a third of all patients complain of *abdominal pain* or *constipation* The occurrence of *diarrhea* is more likely caused by purging than the infection itself The only definite and tangible symptoms of the prodromal period are *chills which occur in about 20 per cent of cases* and *epistaxis* which is encountered in another 20 per cent

During the incubation period the patient is usually ambulatory He has sampled household medications such as analgesics for the headache tonics for the anorexia and cathartics for the constipation Physical examination reveals no abnormality There may however be *slight elevation of the rectal temperature* and the tip of the *spleen* may be just palpable The blood count may show slight *leukopenia* with a relative leukocytosis but except in the presence of an epidemic there is nothing characteristic in the clinical or laboratory examination by which the diagnosis can be made See *Differential Diagnosis of Cryptogenic Fevers* (p 26)

Invasion —Following the period of incubation the bacteria invade systemically and the *blood culture* becomes positive There is a progressive increase in the *temperature* the evening reading rising each day a degree or a degree and a half over that of the previous day until it reaches 103 to 106° F

A clinical observation of great diagnostic importance is the failure of the pulse rate to keep pace with the rising temperature resulting in a *relative bradycardia* With a temperature of 103° to 104° F and a pulse expectancy of 120 to 130 the actual pulse rate may be but 80 or 90 beats per minute The pulse is of good volume and the blood pressure readings are normal but there is observed characteristically a *dicrotism* of the pulse which if sought is easily detected

The *malaise* and *lassitude* of the period of incubation increase during the phase of systemic invasion *Anorexia* and *headaches* continue The hyperemia of the lymphoid patches in the ileum gives rise to more pronounced *abdominal pain distention* and a tendency to *constipation* unless preliminary purging has caused sufficient inflammation of the mucous membranes to result in a persistent diarrhea Toward the end of the first week *splenic enlargement* becomes more obvious and there is often a catarrhal inflammation of the bronchi giving rise to a persistent *cough* The respiratory symptoms and signs may dominate the clinical picture to the point where older clinicians spoke of *typho pneumonia*

Rose Spots —The characteristic rose spots due to bacterial emboli in the skin appear toward the end of the first week or the beginning of the second The typhoid roseola consists of small pinkish papules which fade on pressure The papules appear in crops of from 3 to 40 persist for a few days and then disappear Most commonly they are found over the upper abdomen the lateral lumbar region and on the back (See Fig 25)

The laboratory diagnosis may be made definitely at this time since

ingococcic meningitis The severity of the invasion and its tragic after maths justify overzealousness in the use of specific therapeutic measures We prefer an initial intravenous administration of *sodium sulfadiazine* with subsequent oral doses and intramuscular and intrathecal instillations of *penicillin* Our third choice is for the use of *serum* in the severely toxic and in the inconsequential number of individuals who do not respond to anti infective agents

Supportive Therapy—Because of the frequent manifestations of shock exemplified in the highest degrees in the Waterhouse Friderichsen Syn drome the use of the anti infective agents is supplemented by injections of *adrenal cortical extract* (p 1267) using 2 to 10 cc with each injection of the anti infective agent the dose depending on the degree of shock and the quality of the response In extreme instances 50 to 100 cc may be re quired *Plasma* and *sixth molar sodium lactate* may also be used as in the treatment of shock (p 938)

The Continuous Intravenous Drip—In the severely toxic instance of men ingococcemia or cerebrospinal meningitis the multiplicity of therapeutic agents which is required makes for technical difficulty unless a continuous intravenous drip is established With this method the therapeutic program may be executed with comparative ease The suggested infusates include 100 cc of 5 per cent sodium sulfadiazine 250 cc of plasma if shock is a presenting problem and the priming dose of penicillin in a solution of which each cubic centimeter contains 1000 units after the active agents have been introduced the drip is maintained with physiological saline or 5 per cent dextrose in saline until subsequent doses of anti infective agents or plasma are required

Prevention—Preventive treatment of contacts in epidemics of meningo coccemia and cerebrospinal meningitis is accomplished by oral doses of *sulfadiazine* While case incidence is comparatively low it is better to treat an entire population than miss a single potential victim The dose of sulfadiazine is 2 gm (30 grains) given in doses of 0.5 gm ($7\frac{1}{2}$ grains) four times daily until all danger has passed The usual precautions against sulfonamide toxicity are observed the patient is warned to take bicarbon ate of soda with the sulfonamide as well as a full tumbler of fluid

THE GONOCOCCUS

Neisseria gonorrhoeae is responsible for an estimated 1 000 000 acute infections annually in the United States as well as for an amount of chronic ill health disability sterility and unhappiness that is beyond estimation

Bacteriology—Gonococci are gram negative cocci arranged in pairs with adjacent sides flattened or slightly concave giving each organism a characteristic coffee-bean shape The individual coccus is about 1.5 microns in the long diameter and 0 8 micron in width It is non motile and does not form spores or possess a capsule The resistance of the gonococcus to heat, light and chemical agents is slight A temperature of 41 to 4 C kills the organism in two hours The gonococcus is destroyed by most disinfectants in high dilution and is particularly sensitive to silver salts (p 134) a fact of therapeutic importance Complete drying quickly kills the organism but when incompletely dried and protected from light it may live on clothing bedding and toilet articles for several hours The latter fact is of importance in the spread of vulvovaginitis among children in hospital and institutional wards

The gonococcus is parasitic exclusively for human tissue Attempts to produce infection by the direct inoculation of organisms on the conjunctival and urethral mucosa of anthropoid

On or about the fifth or sixth week the patient is afebrile and urine and stool cultures are free from organisms An exceedingly weak and debilitated patient is ready to initiate the struggle for complete restitution of health and strength

Relapses and Recrudescences

Following the restoration of normal temperature relapses and recrudescences may be experienced In the recrudescence the temperature rises *suddenly and remains elevated for a few days without definite complaints* or findings

The *true relapse* consists in a repetition of the original disease of shorter duration and lesser intensity The febrile relapse rarely continues for more than two or three weeks and during its course the essential features of the initial disease are reproduced including the laboratory findings the positive blood cultures the enlargement of the spleen and the appearance of rose spots Complications such as perforation and hemorrhage are unlikely to occur during a true relapse and the prognosis is generally good

Clinical Variations

The variations in the clinical course of typhoid fever are manifold The onset may be heralded by a *chill* suggesting a *pulmonary infection* while the early occurrence of catarrhal bronchitis further strengthens that impression The onset may be characterized by *headache* and *delirium* suggesting *meningitis* or there may be *diarrhea* as in the *dysenteries*

The entire course of the disease may be so mild that the patient remains ambulatory throughout So called *walking typhoid* is a likely source for widespread dissemination of the organism since no precautions are taken and the patient mingles freely in the community

In observing the course of the temperature reaction the physician encounters many troublesome vagaries The disease may be initiated by a *chill* and terminate by a *crisis* A sudden and precipitous *fall in temperature* particularly in the second or third week gives rise to the suspicion of an intestinal hemorrhage while a *sudden rise in the temperature* at this time suggests the development of a complication which may be intra abdominal pulmonary, or phlebitic *Hyperpyrexia* is usually a terminal event

After the acute stages of the disease are over a *continued subfebrile course* may persist without demonstrable findings Under these circumstances arteritis or venous thrombosis should be suspected In convalescence a *persistent hypothermia* may be observed This is commonly associated with a lowering of the basal metabolic rate and may be marked by a gain in weight and loss of hair

Diagnosis

The diagnosis of typhoid fever is a laboratory discipline rather than a clinical exercise The practitioner should confirm his tentative diagnosis by *bacteriologic* and *serologic* data If private facilities are inaccessible governmental services are available throughout the United States

In the course of an epidemic the recognition of typical typhoid fever offers no difficulty Pending laboratory confirmation the presumptive

position The clinical problems that arise as a result of these manifestations are included in the chapters on the female reproductive system (p 2477)

The remaining local inflammatory infections of gonorrheal origin consist of *ophthalmia* which is most common in the newborn and strangely infrequent in adults See *Diseases of the Eyes* (p 1621)

Gonococcemia —In a relatively small proportion of individuals afflicted with local gonorrheal infections a bacteremia develops in from three to five weeks after the primary infection Occasionally gonococcemia may also arise late in the course of the localized process Whether the bacteremia results from unusual virulence of the infecting strain a lack of tissue resistance or the trauma of rough instrumentation is unknown

Invasion of the blood stream is suspected when constitutional symptoms arise in the course of a local process The patient develops a febrile reaction chills or manifestations of metastatic infection next to be described The diagnosis is definitely established by *blood culture* which requires the aid of the trained bacteriologist because of the difficulties inherent in growing the organism on laboratory media

Metastatic Gonorrheal Manifestations —Metastatic gonorrheal manifestations occur in the patient who suffers an obvious bacteremia but they are often seen in those who deny a recent venereal infection and in whom no evidence of local gonorrheal disturbance can be found The commonest sequels of gonococcemia are *arthritis tenosynovitis periostitis endocarditis meningitis* and *dermatoses* which are described in later sections of these volumes

The metastatic complications of gonococcemia are to be treated vigorously by systemic forms of therapy with due appreciation of their pathogenesis The general principles of treatment are outlined in the succeeding paragraphs

DIAGNOSIS

The diagnosis of gonorrhea is often too lightly considered in clinical practice It is generally assumed that urethritis is gonococcal until proved otherwise While this viewpoint is usually correct the practitioner must not expose his patient or himself to the possibility of error since far reaching consequences bearing on marriage divorce and human happiness may be involved

Smears —The diagnosis of gonorrhea most often is made on the results of microscopic examination of stained smears To obtain organisms for smears sterile cotton tipped swabs are applied to the urethral discharge cervix Bartholin s abscess conjunctiva or wherever the suspected lesions may be The swab is rolled (not streaked) on a clean glass slide which is then dried in the air gently fixed by heat and stained by Gram s method When viewed under the microscope gonococci are characteristically seen as gram negative kidney or coffee bean shaped diplococci within the cytoplasm of polymorphonuclear leukocytes (Fig 8 p 47)

The use of smears in the diagnosis of gonorrhea has many practical limitations It may not be possible to demonstrate the organisms in chronic gonorrhea especially in females Moreover modern treatment with sulfonamide drugs rapidly produces negative smears often leading to the erroneous conclusion that the disease has been cured In *nonspecific ureth*

not cause confusion because the titer is highest for the actual infecting organism and lower for the antigenically related strains

The Blood Count —During the prodromal period and the first weeks the red count is normal and the fever is unaccompanied by leukocytosis There is in fact a *leukopenia* with a relative *lymphocytosis* The leukopenia persists throughout the disease unless there occurs an acute inflammatory complication such as peritonitis in which event the sudden development of leukocytosis is of great diagnostic value

The red cells and hemoglobin fall progressively particularly during the second and third weeks of the disease when there is considerable loss of blood from the ulcerated areas of the intestinal mucosa With acute bleeding the red cells may sink to levels as low as 2 000 000 per cu mm the hemoglobin falling proportionately

Complications

The two dreaded complications of typhoid fever are perforation which occurs in approximately 3 per cent of all cases and significant hemorrhage which is an incident in approximately 7 per cent These mishaps take place at the site of ulceration of the intestinal mucous membrane generally in the ileum and are most likely to occur during the second or third week of the disease Clinically perforation and hemorrhage are usually accompanied by prodromal symptoms which consist of diarrhea distention and grumbling abdominal pain

Hemorrhage —When massive hemorrhage is encountered the first indication may be the presence of gross blood in the stool but more commonly the visible evidences of bleeding are preceded by systemic evidences of *exsanguination* The patient suddenly collapses or complains of faintness The temperature falls precipitously while the pulse rate rapidly mounts

Treatment must be initiated immediately Blood volume can be restored and maintained with an intravenous drip of glucose saline or plasma until citrated whole blood can be obtained There are some who argue that intravenous therapy is contraindicated because of the danger that the added fluid elevates blood pressure and thus favors continuation of bleeding by dislodgement of the clot As a matter of fact the continuous intravenous drip restores tension to normal levels but never higher The concept of a clot blowing out is unphysiological and contrary to clinical experience

Perforation —The most characteristic feature of perforation is the sudden onset during the second third or fourth weeks of *sharp abdominal pain* of increasing severity This is not to be confused with the abdominal pain and tenderness which are present during the first week or ten days and abate before the phase of possible penetration Impending perforation is suspected when abdominal pain recurs toward the middle or the end of the second week or during the third wek

The pain of perforation is most frequently in the *hypogastrium* to the right of the midline at a point corresponding to the site at which the terminal ileum approaches the ileocecal junction When the suspicion of impending perforation arises the patient must be removed to a hospital as quickly as possible The practitioner summons his surgical consultant

diamine hydrochloride turns them first pink then red and finally black If plates containing mixed organisms are flooded with a fresh solution of this dye the gonococci can readily be distinguished by their color reaction Streptococci and diphtheroids do not give this reaction Colonies which morphologically appear to be gonococci and are oxidase positive should be picked from the plate and smears made to check their morphology

Colonies may also be inoculated into semi solid ascitic fluid or serum agar to which various carbohydrates have been added The gonococcus ferments dextrose but does not ferment maltose sucrose or lactose

Complement Fixation Tests—The best available serological test for the diagnosis of gonococcal infection is the complement fixation test Although there are conflicting reports of its reliability experienced workers using a standard technic assert that the test is frequently helpful and generally reliable but by no means infallible It probably does not compare in accuracy with the Wassermann test for the diagnosis of syphilis but in our experience the test is a useful procedure and should be used more generally In obscure conditions it has frequently proved of great diagnostic value

The complement fixation test does not become positive for several weeks after infection and hence is of little or no value in the diagnosis of acute infection However it is especially useful in arthritis salpingitis and other chronic gonorrheal infections in which the organisms cannot readily be obtained for diagnosis by smear and culture False positive reactions are uncommon but the test may sometimes be negative in the presence of proved gonococcal infection In general the complement fixation test has more positive than negative value

The complement fixation test has been used as a criterion of cure Here it has limited value since it may remain positive for several months after cure has been achieved However when the test has been positive and then after a period of months becomes negative it may be assumed that all foci of infection have been eradicated It should be pointed out that if gonococcal vaccines have been used the test is rendered valueless since they produce sufficient antibody to give a positive reaction Meningococcus infection because of the antigenic similarity of the two organisms will also give a positive test but this should rarely cause confusion

TREATMENT

Previous to the era of successful chemotherapy the prophylaxis of gonorrhea was reasonably satisfactory but curative measures were many and diversified They consisted almost exclusively of local and topical measures of bewildering variety and questionable efficacy Complications were many and frequent Some resulted from the extension of infections due to the virulence of the organism but others were unquestionably the result of overzealous and well intended measures of treatment

PREVENTION

Prophylactic treatment is employed against the ophthalmia of the new born and genital infections of venereal origin

Ophthalmia Prophylaxis—The preventive treatment of gonococcal infection is most eminently successful in the prevention of ophthalmia Most

the enteric phase from *ulceration* and *spreading peritonitis* or from *exsanguination* as a result of massive hemorrhage In uncomplicated cases death results from a *progressive toxemia* The patient alternates between profound stupor and muttering or mild delirium with involuntary passage of urine and feces Progressive circulatory failure and terminal pulmonary complications follow

The overall mortality rate of typhoid fever is about 10 per cent In infants and in individuals past the age of fifty, the mortality rate is considerably higher The coexistence of chronic or debilitating disease naturally adds to the gravity of enteric fever

Specific Treatment

The introduction of streptomycin (p 104) provided the first hope for successful specific treatment in typhoid fever Comparatively large doses of the antibiotic agent must be given for long periods of time both by oral and parenteral introduction Orally introduced streptomycin is not absorbed from the intestinal lumen and it successfully rids the stool of the pathogen Four or five divided doses to total 500 000 and preferably one million units daily are given in combination with an equal amount introduced by intramuscular injection or continuous intravenous drip For intramuscular injection 500 000 units in saline solution are injected intramuscularly six times daily at four hour intervals For the continuous intravenous drip the total of 2 000 000 units may be dissolved in 3000 cc of saline delivered at a rate of 3 cc per minute Treatment must be continued for at least seven and preferably fourteen days lest relapse or recurrence be encountered Initial results of therapy are disappointing and as a result probatory therapy with an insoluble sulfonamide may be attempted Our choice is sulfathalidine (p 101) using an initial dose of 6 0 gm (90 grains) and daily totals of 6 0 to 14 gm (90 to 200 grains), in six divided doses Penicillin therapy offers no hope for significant efficacy unless in the presence of perforation the peritoneum be invaded by a penicillin sensitive organism such as a hemolytic streptococcus (p 160)

Nonspecific Treatment

More than any other disease typhoid fever requires intelligent and diligent nursing care After the physician has left his initial orders, there remains little for him to do throughout the course of the disease beyond seeking early evidence of complications and instituting the necessary treatment for *hemorrhage* (p 234) or *perforation* (p 235)

The physician is wise if he undertakes two important preliminary precautions The first is to type the patient s blood and have a *compatible donor* available in the event of the necessity for immediate transfusion Additionally he should summon his *surgical consultant* Should abdominal sepsis or complications arise the surgeon is in a better position to assist in the diagnosis and recommend the optimal operative procedures

Hydrotherapy —The general management of typhoid fever has undergone changes of simplification in recent years The allegedly specific hydrotherapeutic methods of the Brand tub bath and the use of ice coils have fortunately been discontinued The former particularly was time and energy consuming and depleted patient and attendants

Diet —The principle of *high calory feeding* has replaced the starvation regimen of the dark past For the most part the patient is given soft and

are 1 gm (15 grains) at four hourly intervals day and night for five days until a total of 33 gm has been administered With each dose of the sulfonamide the patient takes a teaspoonful of bicarbonate of soda and a full glass of fluid Each urine voiding is examined grossly turbid or discolored specimens are saved for laboratory examination A hemogram is made on the day following the initiation of therapy and at least once more during the course of the treatment Local treatment is strictly avoided the patient need be given no other directions except for avoidance of sexual intercourse and sexual excitement The sulfonamide-treated patient is reexamined at the end of five days and a successful issue is observed in 50 to 90 per cent of the group the figures varying with different reports The less favorable response is particularly worthy of note in general practice since many patients believe that the sulfonamide cure for gonorrhea is absolute and that no other measures are required Those patients who do not respond to a single course of oral sulfonamide may be given a repeat course using an other preparation in the event that the organism is fast or penicillin may preferably be substituted

Penicillin (p 106) is the preparation of choice in the treatment of gonorrheal infections Using an initial intramuscular injection of 100 000 units subsequent three-hour doses of 50 000 units are given until 500 000 units and preferably one million units have been delivered The purpose of the larger dose is to effect simultaneous prophylaxis against a possible concurrent exposure to syphilis (p 331) With massive penicillin therapy smears are negative within a few hours cultures are sterile shortly thereafter the discharge disappears after the third or fourth injection and the percentage of cure approaches 100 When it is impracticable to give three hourly injections the saline solution of penicillin may be replaced by the oil wax preparation using 300 000 units every six or eight hours for a minimum of four doses Despite the splendid results of penicillin therapy an occasional organism may lurk in the urethra following therapy The patient is warned to return for a culture in a few days Intercourse is forbidden until there have been at least two or three negative reports Wassermann tests are taken at fortnightly intervals for at least four months

Combined treatment with sulfonamide and penicillin has advocates provided that the precautions demanded by sulfonamide therapy are followed (p 101) Oral doses of sulfadiazine may be supplemented by intramuscular injections of penicillin in saline or the oil wax mixture using the doses given in the preceding paragraphs

In the treatment of *sulfonamide resistant gonorrhea* penicillin is administered according to the dosage schedule mentioned above We do not favor oral penicillin because of the uncertainty of its absorption and the significantly lower percentage of reported cures Local treatment is avoided under any circumstance since instrumentation results in an increase in complications Curiously enough penicillin therapy is as successful in chronic gonorrhea and its complications as it is in fresh infections

The principles of anti infective therapy that apply to gonorrheal urethritis in the male are equally utilized in the treatment of the female and the management of ophthalmia neonatorum (p 1621)

Hyperthermia —It has already been established (p 217) that gonococci are quite susceptible to heat In the test tube they are killed by exposure to a temperature of 41 or 42 C With this observation in mind various

patient and his ability to cooperate more successfully in general treatment and with the diet Opponents regard the febrile reaction as a defensive mechanism and intimate that the use of the antipyretic drugs tends to defeat the natural protective agencies aimed at the elimination of the invader Our viewpoint is intermediate we do not favor the routine use of antipyretic drugs since they may actually produce nausea and vomiting but neither do we permit our patients to be uncomfortable from an excessive febrile reaction It is our custom to employ hydrotherapy by sponging each time that the temperature reaches 103° F If a successful 'sponge drop' is not obtained acetylsalicylic acid is given half hour before the next sponge to supplement the hydrotherapeutic measure

Treatment of Nervous and Mental Symptoms—In the later weeks of a typhoid fever it is not unusual for the patient to become delirious or exhibit a marked amnesia In the first instance *hydrotherapy* and *sedation* prove to be of great efficacy If there is a suspicion that the mental change is the result of avitaminosis the soluble portions of the *vitamin B complex* are given parenterally The exhausted patient is often fortified by a *transfusion* of citrated blood by the drip method (*q v*)

Treatment of Phlebitis —The frequency of phlebitis in convalescence may be lessened by urging the patient to move the feet and toes throughout the course of the febrile illness The nurse is instructed to encourage these exercises at frequent stated intervals

PREVENTIVE TREATMENT

Preventive treatment of typhoid fever beyond measures that are the province of the public health authorities involve inoculation of the civilian population and the active treatment of carriers

INOCULATION

The value of inoculation against typhoid fever has been established beyond question by the experience over many years of the United States Army For example during World War I when compulsory inoculation was performed on all troops there were 1065 cases of typhoid fever and 156 deaths Russell estimated that if the conditions of the Spanish American war had prevailed when vaccination was not practiced 68 164 men would have died of typhoid fever

The usual method of administration is to give three *subcutaneous injections* in the upper arm at weekly intervals The dosages are 0 5 cc 1 cc and 1 cc More recently *intracutaneous injection* of the vaccine has been recommended Reactions are minimal or absent and the immune response is if anything better than by the subcutaneous route The dosage is 0 1 cc 0 15 cc and 0 2 cc at weekly intervals *Oral administration* of typhoid vaccine has been used widely in Europe but has never found favor in this country its efficacy remains doubtful and its use is not recommended

The *duration of immunity* following vaccination is difficult to determine The titers of agglutinins probably are not directly translatable into terms of actual immunity since in the final analysis immunity to typhoid is a response of the tissue cells not the humoral antibodies Recent work shows that the injection of 1 cc subcutaneously or 0 1 cc intra

CHAPTER 6

BACILLARY INFECTIONS ENTERIC BACILLI

Typhoid (*Eberthella typhi*)
Paratyphoid (*Salmonella*)
Dysentery (*Shigella*)
Colon Bacillus Infections (*Escherichia coli*)
Cholera (*Vibrio comma*)

TYPHOID FEVER

Typhoid fever is an infectious disease resulting from the invasion of the body by a specific Salmonella organism (*Eberthella typhi*) The clinical manifestations are dependent upon a bacteremia with subsequent localization in the intestinal tract gallbladder spleen liver bone marrow and other organs The pathological reaction to the infection consists in a focal necrosis particularly in relation to cells of the reticulo endothelial system

Typhoid fever was once one of the most prevalent of infectious diseases in the past thirty years however the application of the principles of preventive medicine and sanitation has reduced its urban incidence to negligible proportions although in certain rural areas it is still endemic and occasionally epidemic

Bacteriology —The typhoid organism is one of a large group of morphologically indistinguishable gram negative bacilli which may be present in human excreta Some of these bacteria such as the colon bacillus are normal inhabitants of the intestinal tract, whereas others such as the typhoid and paratyphoid organisms (members of the large group of Salmonella) and dysentery bacilli are actual or potential pathogens

Separation of Fecal Bacteria —The separation and identification of pathogenic and nonpathogenic fecal organisms require specially devised bacteriological technics of which the practitioner must have a general knowledge if he is to interpret correctly the findings in a given case For the most satisfactory results the stool or urine specimen should be submitted to the laboratory within two or three hours after it has been obtained If this is not possible approximately 1 gm of material should be added to 8 to 10 cc of a solution of 30 per cent glycerol in buffered saline and placed in a stoppered specimen bottle The glycerin solution tends to inhibit the overgrowth of colon bacilli and other nonpathogenic organisms

Differential Media —When the specimen is received in the laboratory a suspension of the stool or urine is plated on various differential media which take advantage of the fact that nonpathogenic organisms such as the colon group ferment lactose while pathogens with certain exceptions do not Colon bacilli growing on the surface of the medium produce acid from the fermentation of lactose and change the color of the indicator dye In consequence the colonies of lactose fermenting organisms are colored whereas those of the pathogens which do not ferment lactose remain grayish or opaque white

Selective Media —In addition to differential media selective media are also employed These contain chemicals or dyes which partly inhibit the growth of colon bacilli and favor a relatively purer growth of pathogenic organisms For the isolation of typhoid organisms the most highly selective medium is Wilson Blair's although no one medium is optimal for all enteric pathogens

Choice of Media —In dealing with an unknown specimen it is essential that several different media be seeded After twenty four to forty-eight hours incubation suspicious colonies are picked and inoculated into the butt and onto the surface of Krumwiede's agar slant tubes which contain dextrose lactose sucrose and an indicator dye By producing or failing to produce acid and/or gas in this medium pathogens and nonpathogens are separated The latter are then eliminated and pure cultures of the pathogenic organisms are inoculated into

DIFFERENTIAL DIAGNOSIS OF

Food Poisonings

Food poisoning is very frequently encountered in clinical practice Usually the practitioner sees cnly the more severe examples His problem is augmented by the additional symptoms caused by well intended but ill advised purging for the alleged ptomaine

CAUSE	DIAGNOSTIC FEATURES
Chemical	
Antimony	Vomiting a few minutes after ingestion of food cooked in gray-enameled or galvanized utensils (p 752)
Cadmium	Vomiting and diarrhea a few minutes after drinking liquids prepared in cadmium plated refrigerator trays pitchers etc (p 753)
Sodium Cyanide	Weakness coma and respiratory failure a few minutes after eating from utensils cleaned with silver cleaner
Sodium Fluoride	Vomiting abdominal pain diarrhea convulsions and paralyses a few minutes to two hours after taking roach powder mistaken for baking powder baking soda or powdered milk
Zinc	Gastric distress abdominal pain nausea vomiting and diarrhea a few minutes after acid drinks from galvanized iron utensils (p 761)
Poisonous Foods	Vomiting and abdominal pain a few minutes after ingesting mussels clams white bait fish milk from cows grazing on snake root, water hemlock raw sprouted potatoes or rhubarb leaves
Ergotism	Headache convulsions and peripheral vascular disturbances including gangrene after eating spoiled rye (p 955)
Mushroom Poisoning	Vomiting diarrhea abdominal pain and convulsions 6 to 15 hours after ingestion
Favism	Fever anemia hematuria and jaundice within 1 hour after eating fava bean
Infection	
Staphylococcal	Vomiting diarrhea and abdominal cramps 1 to 6 hours after ingestion of food Usually epidemic after taking pastry fillings sauces etc (p 153)
Salmonellar	Abdominal pain, chills fever vomiting and diarrhea 7 to 12 hours after taking cold meats or salads Epidemic (p 239)
Streptococcal	Nausea abdominal pain and diarrhea 5 to 18 hours after food
Botulism	Dysphagia diplopia and respiratory paralysis 18 hours to 4 days after home canned food (p 311)
Bacillary Dysentery	Mild to severe diarrhea with isolation of organisms in stools (p 243)
Amebic Dysentery	Mild to severe diarrhea with identification amebae in stools (p 523)

broth containing a variety of sugars Typhoid Salmonella and various types of dysentery organisms differ in their ability to produce acid and gas in various sugar substrates and may be tentatively identified by the reactions summarized in Table 21

Rough and Smooth Variants—Typhoid colonies may be "*smooth* (S) or *rough* (R) and this property is associated with virulence since the latter (R) are usually relatively avirulent. The virulence of smooth strains of typhoid bacilli appears to be associated with the presence of a heat labile *Vi antigen* present in all organisms recovered from typhoid patients and from most carriers

Toxins—The typhoid bacillus does not produce an exotoxin and the various properties of the endotoxins are merely the effect of the various *somatic antigens* (p 143) of the bacterial bodies themselves For example fever and leukopenia two characteristic features of typhoid fever can be produced in normal human volunteers by the intravenous injection of somatic extracts of typhoid bacilli containing O and Vi antigens Since these fractions are antigenic it would seem possible theoretically to produce an antibacterial therapeutic serum Unfortunately in practice such sera have thus far proved clinically ineffective

Epidemiology—Epidemics of enteric fever result from the pollution of *water milk* and *food supplies* Whatever the method of transmission the ultimate cause of the infection is the patient or healthy carrier whose excreted urinary or fecal bacilli have fouled the ingesta of the community Waterborne epidemics formerly of common occurrence are characterized by an explosive onset in an entire community persons of all ages and both sexes developing the disease within a relatively short time Because the typhoid bacillus is resistant to cold epidemics have arisen from the ingestion of *polluted ice*

Epidemiologists have received information from the studies of the *specific bacteriophages* which appear in the feces and have the ability to lyse the specific organisms The bacteriophage is so highly specific for each strain of organism that it is possible to classify seemingly identical typhoid bacilli on the basis of their susceptibility or resistance to various bacteriophages By this technic strains of bacilli isolated from different cases of typhoid fever may be identified to determine whether or not they came from a common source of infection

Before pasteurization was widely practiced *milk transmitted epidemics* were common Oysters and lobsters which are often bred in sewage polluted waters have been incriminated as the sources of numerous epidemics *Food borne epidemics* usually confined to patrons of a single restaurant or the participants at a large upper result from infection transmitted by the contaminated fingers of a carrier food handler A classic example is the case of the famous typhoid Mary a cook who was responsible for about 1300 cases of typhoid fever over a period of a number of years

Epidemics of *water borne typhoid fever* are most common in late summer and fall but small epidemics and endemic infections from food polluted by carriers occur at any season of the year including winter Although all age groups are susceptible the highest incidence of the disease occurs in children and young adults from ten to twenty five years old While there is no striking difference in the incidence of the disease in the two sexes there is a preponderance of women among chronic carriers This may be related to their tendency to develop cholecystitis since the gallbladder is a favorite nest for typhoid bacilli

The improvement of general sanitary conditions of living and specifically the purification of water supplies and the pasteurization of milk have tremendously reduced the prevalence of typhoid fever This has occurred to such an extent that medical schools located in metropolitan areas have difficulty in finding patients suitable for teaching purposes In rural communities sanitation has lagged and there endemic areas of typhoid fever still exist

Carriers—Following any epidemic numerous infections arise secondarily from contact with primary cases of the disease or with carriers After clinical recovery from typhoid fever 3 to 5 per cent of patients continue to excrete bacilli in the urine or stool for more than two months Chronic carriers may harbor organisms for as long as twenty five years The excretion of bacilli may be intermittent so that cultural examinations of a suspect must be repeated at intervals for long periods

Many chronic carriers give no history of frank typhoid fever Since it is known that in a single common source epidemic the host reaction to the infection depends upon the size of the infecting dose and the immune status of the individual some of these healthy carriers may have had merely a mild gastro intestinal upset or no symptoms at all

Immunity—The immunity to typhoid fever is best measured by the presence of agglutinins in blood serum The recognition of these antibodies constitutes the basis for the *Widal reaction* which is of such value in diagnosis

S SCHOTTMUELLERI (PARATYPHOID B)

S schottmuelleri is frequently isolated in the United States It most often produces attacks resembling mild typhoid fever but it may also result in the food poisoning syndrome (p 240)

S ENTERITIDIS

S enteritidis as its name implies produces acute attacks of vomiting and diarrhea It is one of the most frequently encountered types of Salmonellae

S TYPHIMURIUM (AERTRYCKE)

S typhimurium is probably the Salmonella organism isolated most frequently in food poisoning' epidemics in the United States

S CHOLERAE SUIS (SUIPESTIFER)

S cholerae suis (*suipestifer*) is responsible for both sporadic and epidemic disease The *epidemic form* has a brief incubation period and an abrupt onset with headache fever abdominal cramps vomiting and diarrhea Recovery is fairly rapid and there is a negligible mortality rate The syndrome differs in no way from food poisoning caused by other Salmonellae *S suipestifer* infections also occur *sporadically* producing a number of different clinical manifestations These types of suipestifer infections are becoming more frequently recognized although it is doubtful if there has been a true increase in their prevalence

The sources of infection and the portals of entry are rarely known In sporadic cases bacteremia is common and the diagnosis is usually made by the blood culture The most frequent clinical type of infection is a *typhoid like syndrome* without localizing signs of infection and with an acute onset high fever lasting two to ten days headache anorexia vomiting abdominal pain and cough Rose spots are rare Shaking chills and joint pains are encountered and in children meningismus may be present at the onset Leukopenia is noted as a rule but if localization of the infection occurs a leukocytosis occurs In the typhoidal variety blood cultures are positive but the stools and urine are generally negative Specific agglutinins develop in two to three weeks

With or without a preceding typhoidal course *localization of the infection* may occur in various organs The sites of predilection are the *lungs* (33 per cent) *joints* (15 per cent) and *bones* (5 per cent) Bronchopneumonia lobar pneumonia or pleural effusions occur and the organism has even been cultured from bronchiectatic abscesses *Pyarthrosis* and *osteomyelitis* often involving many bones and joints may develop and such cases run a protracted course with a high mortality rate Rarer localizations produce *meningitis subacute bacterial endocarditis pyelonephritis* and *perinephric abscess* It is not always clear whether *suipestifer* is a primary invader or appears secondarily in the presence of chronic disease of various organs The mortality which increases with age approaches 20 per cent among patients under twenty five years of age and rises to 60 per cent in middle aged or older persons

DIAGNOSIS

An etiologic diagnosis of Salmonella infections can only be made by the isolation and identification of the organisms or by the development

Lymph Nodes—The lymph nodes throughout the body especially those of the abdominal mesentery are swollen and their sinuses distended with mononuclear phagocytes In rare instances one of these turgid abdominal lymph nodes may perforate and give rise to peritonitis with preoperative symptoms indistinguishable from those produced by perforation of th intestinal wall

Spleen and Biliary System—The spleen is moderately enlarged soft and deep red Its pulp is strikingly crowded with red cells When splenic enlargement is excessive *infarction and rupture of the spleen* may occur with a resultant peritonitis The diagnosis is suspected when the previously enlarged splenic tumor can no longer be palpated

In the *liver* the typhoid les on is an area of *focal necrosis* that may resemble a miliary tubercle Although the gallbladder is always infected pathological lesions are minimal Bacilli reach the gallbladder very early in the course of the disease Here they find a suitable medium for propagation and pass into the lumen of the bowel to be excreted in the feces Cultures of the intestinal tract show that the bacilli are most numerous in the duodenum and steadily diminish in numbers from above downward so that most of the organisms in the stool are derived from the gallbladder and not from the ulcers in the lower bowel

Bacilli may continue to live indefinitely in the *gallbladder* and result in persistent carrier states Their presence in the gallbladder predisposes to the development of *gallstones* and *chronic cholecystitis* Treatment of the carrier state by cholecystectomy is worthy of consideration when conservative measures fail

Other Manifestations—Inflammation of the *upper respiratory passages* and bronchi occur so commonly in the early stages of the disease as to be regarded as essential features of typhoid fever rather than complications Pneumonia in typhoid fever is rarely due to the typhoid bacilli More often it results from secondary bacterial invasion in the later stages of the disease

Both the *heart* and the *blood vessels* may be affected Toxic degenerat on of the myocardium is encountered in all protracted cases and endocarditis probably occurs more frequently than is usually suspected In the peripheral blood vessels fresh *endarteritis* is present in most fatal cases The involved vessel is a likely site for *thrombus formation* which may produce *embolizations* varying from mild to fatal episodes The left femoral vessels are particularly susceptible to phlebitic changes

The *striated muscles* may show a degenerative change in which the fibers lose their transverse striat ons and become necrotic The lower part of the rectus abdominus the diaphragm and the muscles in the thigh are the common locations for this condition

Chronic suppurative lesions of the tibia sternum, ribs and spine may lead to late osteomyelitis or bone abscess Cultures obtained from these les ons years after the acute attack may show living typhoid bacilli

CLINICAL COURSE OF TYPHOID FEVER

In a typical instance of typhoid fever the clinical course may be described in ill defined phases of incubation systemic invasion enteric fever defervescence complication or death The initial period of *incubation* lasts from eight to twenty three days during which the patient is usually ambulatory The clinical course of the disease is usually dated from the period of *invasion* which occupies the first week to ten days following the termination of the period of incubation It is at this time that *bacteremia* takes place the rose spots appear and bacilli are distributed to the organs of the body The third period of the disease is the stage of *enteric fever* characterized by the localization of the systemic process in the intestinal tract This phase may last from ten days to four weeks and is followed by a period of *defervescence* and *convalescence* in those who are to recover and by *complications* and/or *death* in the severest cases

Incubation —During the period of incubation the ingested bacilli make their way into the intestinal tract of the victim For a period of eight to twenty three days averaging ten days the organisms live in the gut depending for their survival and invasiveness upon factors intrinsic in

other institutions where contamination of a common food source is possible In mental hospitals the carrier rate may be very high Moreover the general carelessness of disturbed patients in personal hygiene favors dissemination of infection There is little satisfactory information in regard to the prevalence and chronicity of dysentery carriers but they undoubtedly exist and play a major role in the transmission of the disease

Immunology—There has long been disagreement as to whether the Shigellae produce toxins It is now agreed that only *Shigella shigae* does so This organism produces a powerful soluble toxin which is antigenic and capable of giving rise to the formation of antitoxin useful in therapy (p 247)

Like the Salmonella group the Shigellae are *antigenically complex* Their accurate serologic diagnosis requires antisera of high titer free of cross-agglutinins The *Shiga* strains are antigenically homogenous and serum prepared against any one strain will agglutinate all strains On the other hand the *Flexner* group is heterogenous and at least four antigenic components (V W X and Z) have been identified Any one *Flexner* strain is a mosaic containing all four antigens in various proportions but each strain contains a preponderance of some one antigen *Sonne* and *Newcastle* strains appear to be antigenically homogenous

As might be anticipated an attack of dysentery confers no permanent immunity and second attacks with the same organism have been known to occur

Pathology—Bacillary dysentery is essentially a localized disease The organisms do not invade the blood stream liver or spleen but remain confined to the *intestine* and *mesenteric lymph nodes* The mucous membrane of the *colon* and the *terminal portion of the ileum* are involved in a diffuse inflammatory process which goes on until necrosis of the mucosa occurs and the dead cells form a false membrane When this membrane separates *ulcers* remain which as a rule are quite superficial The entire mucosa of the intestine including the portions not involved by ulceration is edematous and congested with leukocytes Healing generally results in complete restitution of the mucosa but *scarring* and *stenosis* of the bowel may occur

CLINICAL MANIFESTATIONS

The *incubation period* of bacillary dysentery is usually forty eight hours although it may be as long as seven days For clinical purposes infections may be classified as *mild* moderate *fulminating* and chronic

MILD INFECTIONS

Perhaps the commonest type of dysentery in America is a mild infection which simulates an ordinary *gastro enteritis* with vomiting moderate diarrhea and slight fever There is little evidence of systemic reaction and the stools do not contain gross blood The diagnostic importance of bloody diarrhea in dysentery has been overemphasized since there are many cases with mild diarrhea in which the bacteriologic diagnosis of dysentery comes as a surprise The *Sonne* organism is most frequently responsible for mild attacks of this nature In such cases the stools are likely to be green loose and offensive in odor containing much mucus but little blood See *Differential Diagnosis of Food Poisonings* p 240

While ordinarily of short duration dysentery may last for a month or more The view that ulcerative colitis is a form of chronic bacillary dysentery has not found general acceptance

MODERATELY SEVERE INFECTIONS

In cases of moderate severity the *onset* is sudden with abdominal colic followed shortly by diarrhea Malaise headache prostration and fever occasionally precede *gastro intestinal symptoms* *Soon the stools* consist of mucous shreds and pus and are either pink stained or frankly bloody Fever is generally present Straining tenesmus and abdominal colic accompany each bowel movement of which there may be a dozen a day In

the *blood culture* should be positive although urine and stool cultures are usually still negative

Enteric Fever —At about the time of the appearance of the roseola and the palpable enlargement of the spleen the course of the illness alters in character The features are no longer those of a bacteremia and in fact the blood culture may become sterile and remain so for the rest of the course of the disease unless a true relapse occurs The disease assumes the character of an enteric fever due to the pathological changes that occur in the Peyer s patches resulting in sloughing and ulceration of the over lying intestinal mucosa The abdominal symptoms particularly *distention* pain and *diarrhea* become aggravated

At this time the *Widal test* for the presence of specific agglutinins be comes progressively more positive The urine and feces previously free from typhoid bacilli now contain the organisms in large numbers The



Fig 5 – Ros spots of typho d f v

temperature remains high and more sustained The pulse rate becomes more rapid and loses its dicrotic character

The course of the disease during the third week is quite similar to that of the second week except that the patient is more exhausted Abdominal symptoms become more pronounced and the dangers of *perforation* and *hemorrhage* increase The *heart sounds* are of poorer quality *Nervous symptoms* become more pronounced and the patient may exhibit a dull stupor or a marked delirium with muscle tremors Nutrition is difficult to maintain Tact and patience are required by the nursing attendant to maintain adequate intakes of fluid and food

Defervescence—In the favorable instances the fourth week witnesses the beginning of convalescence The agglutination titer is higher and urines and stools are still positive for typhoid bacilli The temperature fluctuations break lower each day approaching normal levels

The differential diagnosis of dysentery requires a consideration of *mucous colitis* (p 1846) *Salmonella infection, amebic dysentery* and the *nonspecific gastro intestinal disorders* Occasionally abdominal pain is a first symptom of dysentery If it is localized in the right lower quadrant an attack of *acute appendicitis* is simulated However the tenderness in dysentery is usually more diffuse and the rapid development of frank diarrhea suggests the proper diagnosis

f Complications

Complications of dysentery are uncommon aside from a tendency to chronicity Rarely non suppurative sequels consisting of arthritis urethritis and conjunctivitis appear from two to three weeks after the onset of the diarrhea The *arthritis* is characterized by pain swelling tenderness and periarticular involvement of the tendon sheaths of the knees hips and the joints of the hands The joint fluid is slightly turbid but bacteriologically sterile The joint swellings may persist for several months but complete recovery and eventual restoration of function are to be anticipated *Catarrhal conjunctivitis and urethritis* are other rare complications of bacillary dysentery The clinical differentiation of these manifestations depends on a history of a recent diarrheal episode and absence of gonococci in spreads or cultures of the infectious material

Treatment

Symptomatic Treatment

The symptomatic treatment of bacillary dysentery is of prime importance as it relates to *water balance* In infants dehydration and acidosis may develop rapidly and contribute to the appreciable mortality in this age group The practitioner should therefore be prepared to *administer fluid intravenously* For this purpose saline with or without dextrose plasma or other blood substitutes and whole blood transfusions are of value according to specific indications For the ordinary water loss saline solution with or without dextrose suffices If there are evidences of shock plasma is substituted Finally for patients who have been afflicted for a longer period whole blood transfusions are indicated in the presence of the resulting anemia

During the acute stage of the illness it is wise to withhold all oral feedings Reliance may be placed upon the *intravenous drip* As soon as the stomach is tolerant the patient is permitted sips of boiled milk or cocoa and small quantities of boiled rice Gradually the amounts of the fluids and cereals are increased and later the patient is placed on a bland low residue soft diet (p 668) Initial purges and enemas are avoided

Colic and tenesmus are often relieved by *hot compresses* to the abdomen *Antispasmodic drugs* are administered atropine substitutes such as *trasentin* are of particular value (p 3875) The patient is sedated with *phenobarbital* and a *hypnotic* is administered at bedtime If the diarrhea persists and the effects justify the administration of opiates a teaspoonful of Camphorated Tincture of Opium (Paregoric) is given each time there is an evacuation If the diarrhea continues for more than a week subclinical vitamin deficiencies develop and *multivitamin preparations* are added to the diet

clinical diagnosis of typhoid should be entertained under the following circumstances (1) the persistence beyond a few days of a febrile process without localizing manifestations (2) fever with a relative leukopenia (3) fever with a relative bradycardia (4) fever with a palpable spleen (5) fever with a roseola (6) fever with abdominal distress or pain (7) fever with constipation or mild diarrhea (8) fever with headache of unexplained origin (9) fever with malaise anorexia or lassitude

The presence of these suspicious symptoms calls for laboratory assistance by *blood culture serum agglutination reactions stool* and *urine cultures* and *blood counts* With these data at hand there is little excuse for failing to make a definite diagnosis of typhoid fever and there is not much to be gained in clinical deliberations relative to differentiation from other cryptogenic fevers (p 26)

These statements are not intended to give the impression that laboratory data are necessarily definitive Isolation of the bacillus from blood urine or stool usually leaves no doubt as to diagnosis but agglutination tests may be most misleading (p 56)

Blood Cultures —Blood cultures in the first week should yield the bacillus in over 80 per cent of cases By the end of the third week the blood is apt to be sterile except in severe infections and during a true relapse The *agglutination titer* (Widal reaction) does not usually reach its maximum level until the bacteremia abates It supplements the culture report and should be taken at the same time if facilities permit

Urine and Stool Cultures —Urine and especially stool cultures should be positive at all times during the enteric phase at which time the serum agglutination titer is elevated and the blood cultures are sterile

The final recognition of any isolated organism rests upon the results of *serological reactions* Having obtained the organism in pure culture *agglutination tests* are set up by the macroscopic tube method or the rapid slide method using specific sera for each organism For typhoid paratyphoid A and B and for several of the dysentery group (Shiga Flexner Hiss) commercially prepared diagnostic sera are available

Serum Agglutinins (Widal Test) —Typhoid agglutinins to H and O antigens can be demonstrated in the blood serum by different technics Normal persons who have never received typhoid vaccine or suffered from the disease may have low titer agglutinins for both H and O antigens As a result of vaccination the titers of both H and O agglutinins rise but particularly the former Moreover as a result of nonspecific infection with another organism there may be an anamnestic reaction with a rise in titer chiefly to the H antigen Thus a rise in H agglutinin may be *misleading* wherea an *increased titer to O antigen* is of *greater specificity*

It is impossible to define categorically the titers which are significant and diagnostic A rising titer of agglutinins during the course of an infection is of more significance than the actual levels themselves In general O agglutinin titers of 1 300 or more are seen only in typhoid fever Titers of H agglutinins as high as this or higher may follow vaccination

Because of the antigenic similarity of the members of the Salmonella group infection with one of the paratyphoid group may result in an elevation of H and O agglutinins for typhoid Likewise a typhoid infection raises the titer for the related paratyphoid organisms Generally this does

PREVENTIVE TREATMENT

The preventive treatment of bacillary dysentery with vaccines has been disappointing In the presence of an epidemic exposed individuals are entitled to probatory prophylactic chemotherapy with the *soluble* or *in soluble sulfonamides* in the doses employed in active treatment

For the most part the prevention of bacillary dysentery is a public health problem involving the protection and control of carriers and the safeguarding of food milk and water supplies Favorable results have already been reported in carriers by the administration of 3 to 6 daily doses of 10 to 20 gm of *sulfaguanidine* or *sulfasuxidine* A sufficient degree of absorption and toxicity is encountered to necessitate discontinuance of the drug in one patient in ten

PROGNOSIS

The case fatality of dysentery varies tremendously in different parts of the world and in different epidemics In the Orient epidemics with case fatality rates of 10 per cent or higher are reported In the United States the mortality is generally very low except in young and debilitated infants and in inmates of mental hospitals The mortality also varies with the type of infecting organisms Shiga infections are generally most severe Flexner infections are moderately severe or mild while the Sonne organism generally produces only a mild type of disease

The effect of specific chemotherapy on prognosis remains for the immediate future to decide but it may be anticipated that a most favorable decrease in mortality is within the range of possibility

COLON BACILLUS INFECTIONS

Escherichia coli is a normal inhabitant of the lower intestinal tract of man In this site it is nonpathogenic although it may produce disease when it gains access to other tissues

Bacteriology—The colon bacillus is a small *gram negative rod-like organism* It is usually non motile and grows readily on simple laboratory media In the diagnostic bacteriological laboratory colon bacilli must be distinguished from the enteric pathogens such as typhoid, Shigellae and Salmonellae which are morphologically similar This differentiation (p 226) is made by the use of selective and inhibiting media and by the special characteristics of these organisms in regard to the fermentation of various sugars

Immunity—Most persons probably have a good deal of *natural immunity* to the colon bacillus and *bacteriolysins* can be demonstrated in normal blood Whether recovery from an infection such as pyelitis results in the development of immunity is not known Reinfection of the urinary tract is certainly very common but mechanical and other factors probably play a dominant role in determining these phenomena

CLINICAL MANIFESTATIONS

The colon bacillus may be the cause of infection in the urinary and genital tracts the liver and biliary passages or the peritoneum In the vast majority of instances the result is a localized inflammatory process resulting from direct implantation lymphatic or hematogenous spread With surprising rarity a bacteremia results secondarily and then may produce metastatic deposits throughout the organs of the body

Local Inflammatory Lesions—The local inflammatory lesion due to *E coli* are described in the several chapters that deal with the respective system disturbances Thus in the section on the Urinary System (p 2997) are

since *immediate operation is mandatory* for suture of the bowel and drainage of the peritoneal cavity

The *diagnosis* of perforation is made on absolute or presumptive evidence Indubitable perforation with spillage of intestinal content into the free peritoneal cavity is present if abdominal puncture (p 1873) yields fecal material not obtained from hollow bowel or if an x ray of the abdomen taken while the patient sits upright reveals free air under the diaphragm Presumptive evidence of impending perforation penetration or actual perforation may be made on clinical grounds While the danger of a laparotomy on a typhoid patient is not to be minimized the medical attendant should certainly lean towards exploration in doubtful cases rather than hazard a neglected peritonitis

The *clinical characteristics of true perforation* are sharp localized pain with direct tenderness and later when the peritoneal reaction has occurred muscle rigidity with spasm There is an initial rise of temperature and pulse rate the former falling later with the onset of the shock accompanying the peritonitis Leukocytosis is an important sign of developing perforation If operative interference is not attempted the patient develops a generalized peritonitis and usually progresses to a fatal termination

When positive or presumptive evidence of impending or actual perforation exists the patient should be subjected to *immediate laparotomy* The perforation or perforations should be sought in the terminal ileum sutured and the site powdered with 4–8 gm of sulfanilamide Before or during the operation an intravenous drip is set up and the infusion is continued until the patient is safely convalescent With any considerable degree of ileus or as a prophylactic against distention *intestinal intubation* (p 1823) is an inestimable boon

Perforation and Hemorrhage —The association of perforation and hemorrhage may occur It is more likely that the presence of the latter will cloud the signs of the former than vice versa It is a wise precaution to suspect the occurrence of both conditions simultaneously and to supplement the operative treatment of perforation with the use of *blood substitutes* (p 3775) or *citrated whole blood transfusions* Conversely with the surgical consultant the hemorrhaging patient i watched for evidences of peritoneal involvement

Other Complications —In addition to perforation intra abdominal symptoms may arise in typhoid fever from acute cholecystitis and *rupture of the spleen* or of an *abdominal lymph node*

Psychoses (p 1376) often appear in the third and fourth weeks and during convalescence However the introduction of high calory diets and supplementary vitamin feedings have so reduced the number of such symptoms as to point to the inevitable conclusion that the nervous symptoms *peripheral neuritis* and the *myocarditis* of older days belong in the category of nutritional deficiency

Femoral phlebitis and resultant embolizations may occur even late in convalescence The osseous complications including *osteomyelitis* (typhoid spine) and *bone abscess* are late sequels often appearing decades after the acute illness

Death from Typhoid Fever —In typhoid fever death may occur during

Bacteriology—Cholera is caused by a small comma shaped highly motile vibrio The organism is gram negative and grows well on ordinary laboratory media at a slightly alkaline pH It is quite susceptible to the usual chemical disinfectants to heat and drying Organisms in old cultures disintegrate with the liberation of endotoxins but true exotoxins are not formed

Epidemiology—The epidemiology and pathogenesis of cholera are similar to those of typhoid fever (p 227) The habitat of the organism is apparently the intestinal tract of man Infected excreta contaminate food and water supplies transmitting the infection to those who ingest the vibrio laden ingesta Convalescent and chronic carriers are of great importance in the spread of the disease as in typhoid fever (p 227)

Clinical Manifestations

The incubation period of cholera is usually a few days The onset is abrupt with *violent diarrhea* followed by *vomiting* Soon *rice-water stools* become manifest These consist of almost clear water with some mucus and debris The symptoms which follow, formerly ascribed to toxemia are apparently almost wholly the result of profound *dehydration* and *shock* The diarrhea is so copious that the blood volume and extracellular fluid are severely depleted Hemoconcentration falling blood pressure dry skin muscle cramps unconsciousness tachycardia and anuria are the direct results of fluid loss The anuria is of the *pre renal* type (p 2277) There is profound disturbance of the serum electrolytes with loss of fixed base and consequent *acidosis*

The mortality varies from 25 to 75 per cent depending upon the severity of the epidemic and the promptness of treatment

Diagnosis

In an endemic area the clinical diagnosis of cholera is usually obvious The bacteriological diagnosis is made by recovering and identifying the organisms from the *stool* where they are present in great abundance When the organism has been obtained in culture it can be identified by *agglutination* with specific anticholera serum or by the *Pfeiffer reaction* The latter requires a mixture of the organism with complement and anti cholera serum A hanging drop preparation is made and examined Under these conditions the cholera vibriones lose their motility swell and finally disintegrate

Agglutinins develop in the patient s blood but too late to serve as a useful test in diagnosis

See *Differential Diagnosis of Diarrhea* (p 1840)

Treatment

Prevention—The prevention of cholera by measures of *public health control* consists in proper disinfection of the excreta of patients safeguarding water and food supplies and boiling water and cooking food immediately before use

Vaccine—Individual prophylaxis is attempted by vaccination with heat killed organisms The commercial *Cholera Vaccine N N R* contains 1 000 000 000 organisms per cubic centimeter, the vaccine used by the U S Navy contains 8 000 000 000 organisms per cubic centimeter

The technic of injection as employed by the medical department of the U S Navy consists of an initial injection of 0 5 cc and a second injection of 1 0 cc seven or ten days later Thereafter a booster of 1 cc is given

semi fluid feedings with additional calories supplied by added sugar and/or cream An attempt is made to reach 3500 to 4000 calories daily This accomplishment will challenge the ingenuity and patience of the best of nurses In planning the diet it is a good practice to inquire of the patient or the housewife as to individual tastes and dislikes An effort is made to cater to the afflicted individual whose appetite at best will be dulled by the febrile process As a practical matter it is worth while to point out that overzealous stuffing may lead to a rebellion that defeats the objective of all concerned Beyond a little judicious coaxing no strenuous efforts at forced feeding by threats or implications should be permitted

The many devices used to *increase the caloric intake* include adding milk sugar or dextrose to dairy drinks and the fruit juices spreading butter honey or jam on bread adding powdered sugar and cream to cereal serving bacon with egg furnishing ice cream with a syrup or an ice cream soda at least once or twice daily substituting potato spaghetti macaroni or vegetable for the 5 and 10 per cent vegetable using creamed soups in place of clear broths adding whipped cream to desserts and encouraging the ingestion of hard candies between meals

The length of the illness in typhoid fever makes it desirable to use *accessory vitamin feedings* Some of the late complications previously attributed to the disease may well be manifestations of avitaminosis These include bleeding gums neuritis and nervous and mental symptoms

Care of the Digestive Tract—Because of the necessity of frequent and nourishing feedings the intestinal tract requires meticulous care The *mouth and lips* should be tended before and after each feeding The patient is urged to rinse the mouth after meals Dental floss is used to loosen impacted food from between the teeth and chewing gum is provided to keep a flow of saliva in order to prevent *parotitis*

The early tendency to administer a *purge* at the beginning of the fever is to be discouraged as it tends to initiate distention the forerunner of hemorrhage and perforation The bowels are best evacuated daily by a simple soapsuds enema which may be repeated at bedtime if there is any tendency to a feeling of rectal fullness or distention If the stools are dry *mineral oil* is given at bedtime

The importance of *controlling distention* cannot be overemphasized At the first appearance of this symptom the carbohydrate intake is cut down and milk is avoided *Hot stupes* are applied to the abdomen a *rectal tube* is inserted and an *enema* is given These measures will control the difficulty in the vast majority of instances Should they prove insufficient an intramuscular injection of *pitressin* (p 1178) or *neostigmine* (p 3874) is employed using the minimal quantity of the drug that will produce a demonstrable effect within twenty minutes to one half hour

Occasionally patients develop *diarrhea* This disturbance requires active treatment The diet is reduced to the frequent ingestion of boiled milk boiled rice and cocoa one teaspoonful (4 cc) of Camphorated Tincture of Opium (Paregoric) is administered each time that there is an evacuation As soon as the bowel condition has quieted down the normal high calory feeding is cautiously resumed

Antipyretic Drugs—The wisdom of employing antipyretic drugs (p 3832) has been much debated Advocates point to the greater comfort of the

CHAPTER 7

BACILLARY INFECTIONS MYCOBACTERIACEAE

Tuberculosis (*M tuberculosis*)
Leprosy (*M leprae*)

TUBERCULOSIS

TUBERCULOSIS occupies a place of chief medical importance as a cause of clinical disease In the last half century a great deal has been learned about the tubercle bacillus and human tuberculosis Although no specific form of therapy has been evolved measures for the control of the disease have been successful to the extent that the complete eradication of the disease is an attainable goal In 1900 tuberculosis was the leading cause of death in the United States whereas at present it is in seventh position

Bacteriology—The tubercle bacillus one of the group of *mycobacteria* is a slender straight or slightly curved nonmotile organism with occasional irregularities in outline giving it a beaded appearance The organism once stained resists decolorization by mineral acids and is termed *acid fast* *Among the other acid fast organisms are the* leprosy bacillus, Johne s bacillus and various saprophytes (*smegma timothy*) which are of importance only because of their morphological resemblance to the causative agent of human tuberculosis

The tubercle bacillus is essentially pathogenic and so far as is known does not multiply outside the animal body Besides the human strain other varieties include *bovine avian* and *cold blooded* (fish and amphibiae) *types*

Chemistry—Chemical analyses of the tubercle bacillus reveal the presence of lipoids proteins and polysaccharides The *lipoids* consist of glycerides phosphatides and the waxes which are probably responsible for the acid fastness of the organisms *The phosphatide fraction* on injection into animals is capable of calling forth an epithelioid and giant cell reaction The active fraction of the phosphatides appears to be *phthioic acid*

One of the various *protein fractions* seems to be the active constituent of tuberculin and plays a major part in the reaction of tuberculous allergy There is evidence that the protein and the phosphatide fractions are *antigenic* These observations imply that the pathological and immunological reactions of tuberculosis are the result of the action of various recognized fractions of the tubercle bacillus itself and hence there seems no necessity for postulating the existence of hypothetical toxins

Cultivation—Tubercle bacilli can be cultivated on inspissated serum coagulated egg and potato The addition of 5 per cent glycerin enhances the growth of all strains except the bovine While the saprophytes grow rapidly in two or three days the pathogenic strains take several weeks to develop They tend to form tenacious granular clumps in liquid media and crenated colonies on solid surfaces Differences in pigment formation optimum temperature for growth and other characteristics serve to differentiate human bovine avian and cold blooded strains

Resistance—Tubercle bacilli are about as resistant to heat as other nonspore forming bacteria but they are more resistant to chemical disinfectants probably because of their high wax content This explains why sputum can be concentrated by the addition of sodium hydroxide or antiformin without lysing the tubercle bacilli Although the organisms are quickly killed by sunlight they are quite impervious to cold and drying and may survive for long periods making it imperative to adopt strict sanitary measures in the disposal of tuberculous sputa and excretions Five per cent carbolic acid in equal volumes is an active disinfectant after five or six hours

Dissociation—Dissociation of the tubercle bacillus occurs The R (rough) type is quite avirulent and the S (smooth) is definitely virulent The bacillus may have a life cycle including a filtrable form a nonacid fast coccoid form (Much granules) and diphtheroid modifications

cutaneously in a previously vaccinated person will rapidly raise the level of immunity It is suggested therefore that a *booster injection of vaccine be repeated every two years following initial vaccination*

TREATMENT OF CARRIERS

It is the responsibility of health officers to keep track of the whereabouts and occupations of typhoid carriers The practitioner is sometimes confronted with the problem of dealing with these persons so that they may return to such occupations as cooks food handlers and domestic servants

Despite enthusiasm for the use of various dyes and for sulfonamide drugs there is little concrete evidence to prove their efficacy in the carrier states The great majority of typhoid carriers harbor bacilli in the gall bladder and excrete them in the stool An attempt should be made to sterilize the feces with *sulfaguanidine* (p 247) or *sulfasuxidine* (p 247) Failing a permanent disappearance of the typhoid bacillus *cholecystectomy* is advised when the presence of typhoid bacilli in the gallbladder is definitely proven by the cultural examination of the bile obtained by duodenal aspiration (p 3726)

SALMONELLA (PARATYPHOID) INFECTIONS

The typhoid bacillus is only one of the *Salmonella group* of gram negative motile bacilli which may produce enteric disease in man In order of frequency typhoid fever is far less common than infections due to other Salmonella organisms such as *S paratyphi (paratyphoid A) S schottmuelleri (paratyphoid B) S enteritidis S cholerae suis* or *suipestifer* one variety of which is also known as *paratyphoid C* and *S typhimurium (aertrycke)* Besides these an almost endless number of Salmonella organisms have been described and named in various parts of the world in different epidemics and in sporadic cases

Bacteriology and Immunology—See Typhoid Fever p 225

Epidemiology—The spread of human Salmonella infection is facilitated by the fact that many of these organisms are natural pathogens for many animal species as well as man As a result there are many possible sources of infection in addition to the direct or indirect transmission from person to person a fact which accounts for the greater prevalence of Salmonella infections as compared with typhoid fever

S enteritidis a natural pathogen for *pigs* and *cattle* may be present in their tissues at the time of slaughtering It may also be present as a natural and inapparent infection in *eggs* particularly duck eggs *S typhimurium* infects *mice* and *rats* and these animals are frequently chronic carriers disseminating organisms in their excreta

Infection may be *epidemic* or *sporadic* depending on the route of transmission and the method of infection Water milk and food may be contaminated directly or indirectly by human or animal carriers and illness may result from ingestion of animal tissue originally infected

Carriers—*Human* carriers are undoubtedly common but little is known of their actual frequency or of the persistence of the carrier state The problem has been neglected largely because of the mildness of these infections as compared to typhoid fever Paratyphoid A and B and *suipestifer* are probably spread chiefly by human carriers but any of the other organisms may also be propagated in this way

GENERAL CLINICAL MANIFESTATIONS

In man Salmonella may produce a *typhoid like infection* or *acute gastro enteritis* (*food poisoning*) In a single outbreak due to a single type

Pathogenesis—The clinical evolution of tuberculosis depends at every stage of the process upon the action and interaction of the organism and the host The *virulence* of the organism depends chiefly upon the size and frequency of the infecting dose *Resistance* is partly natural and partly acquired *Humoral antibodies* can be demonstrated but do not appear to play an important role in resistance which is essentially a *cellular reaction* and is accompanied by manifestations of *hypersensitivity* to the tubercle bacillus Age sex race,

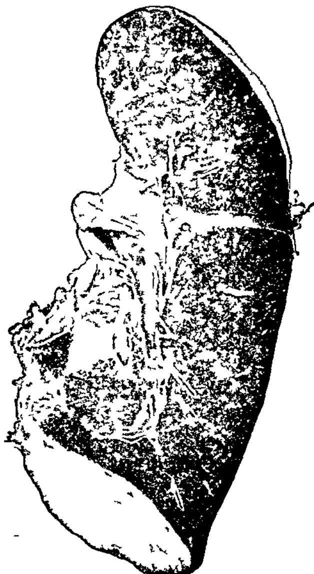


Fig 27—Acute miliary tuberculosis of lung *

nutrition coexistent disease states and endocrine changes such as those occurring at puberty and in pregnancy all have some effect upon the level of immunity In turn the level of immunity plays a *major role in determining the evolution of the disease in the infected individual*

The pathogenesis of tuberculosis is considered in three phases (1) the primary complex (2) the stage of dissemination (3) chronic organ tuberculosis

* MacCallum Textbook of Pathology

Helminthiasis	May be mild diarrhea with identification of ova or parasites in stool (p 537)
Trichinosis	May be mild or moderate diarrhea with eosinophilia myalgia and puffiness under eyes (p 539)
Typhoid Fever	May start with mild diarrhea (p 1840) Isolate organism from blood or stool Get serum for agglutinins (p 59)
Pharmacologic	Overdoses of cathartics (p 1827) Especially with candy medications containing drastics and cold laxatives producing intestinal flu or grippe
Digestive	Following gluttony After drinking bout especially of champagne and wines

of organism there is an acute onset of vomiting and diarrhea in some cases with rapid recovery whereas in others associated constitutional symptoms are present and many patients even suffer a prolonged febrile illness not unlike typhoid fever There is no satisfactory explanation for these variations in symptoms though some organisms in the Salmonella group are more likely to produce one type of clinical disease than another as will be considered subsequently The foods most frequently involved are cold meats and salads

Typhoidal State —The typhoidal state produced by various Salmonella organisms can only be distinguished from true typhoid fever by *bacteriologic* and *serologic* methods Clinically the disease may be as severe as the classical typhoid or mild and abortive In the severer form bacteremia fever splenomegaly rose spots and a prolonged course characterized by relapses and remissions may occur The fever is more apt to be irregular and septic than in true typhoid Leukopenia is generally present Vomiting and diarrhea are more prominent features but the complications of perforation and hemorrhage are rare and the mortality is not more than 5 per cent *Pathologically the intestine is less severely involved* The *usual duration* of the illness is two to three weeks *Treatment* is similar to that of typhoid fever (p 236)

Acute Gastro enteritis (Food Poisoning) —Acute gastro enteritis due to Salmonella organisms is far more common than the typhoidal type of infection The *incubation period* is less than twenty four hours The *onset* is acute with vomiting diarrhea headache fever and prostration The disease rarely lasts more than a week and usually terminates in a few days The severity of the attack varies considerably and may at times consist only of diarrhea without constitutional symptoms In this form of the disease bacteremia is quite uncommon

The disease is apparently confined entirely to the intestinal tract but little is known of the pathology since the mortality is negligible

Clinical Infections by Specific Organisms

S PARATYPHI (PARATYPHOID A)

S paratyphi seldom encountered in America may give rise to the typhoid like picture More commonly however it produces gastro enteritis

The primary infection is of the *exudative type* but, as resistance and hypersensitivity develop it tends to form a *caseous nodule* and may eventually *calcify* From the primary lesion bacilli are transported via the peribronchial lymphatics to the hilar lymph nodes and a *bipolar primary complex* is evolved

In more than 95 per cent of all tuberculous infections the process stops at this point with the lesions undergoing *fibrosis* and *calcification* The calcined nodules resultin from the primary lesions are frequently visible on radiographs and are called *Ghon tubercles* This favorable outcome is the result of a small infecting dose and the rapid and sati factory development of tissue resistance While this process usually occurs in childhood it is no longer uncommon to have the primary complex evolve in adults who come in contact with the organism for the first time

It should be emphasized that the primary lesion develops entirely without apparent signs or symptoms If the infecting dose is heavier or resistance is feeble various clinical manifesta

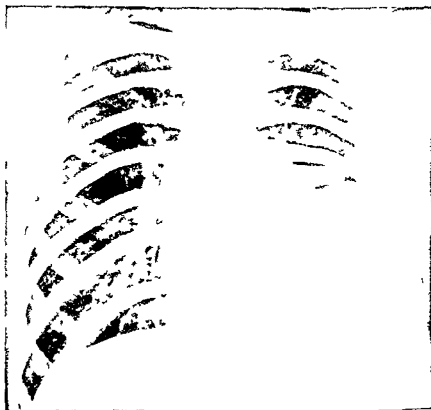


Fig 30—Bilateral increase in hilar markings reticulation of both upper lobes pleural effus n occupying lower third of left pleural cavity in male of 17 years (May 28 1940)

tions of *post primary pulmonary tuberculosis* occur Thus there may be a spread to adjacent areas of the lung from either pole of the complex or from the interpolar lymphatics This process as well as the others which produce cl nical disease are consi lered elsewhere (p 199)

The Stage of Dissemination—The second phase of tuberculosis is the *stage of dissemination* by means of the lymphatics and blood stream Although the great majority of persons manage to arrest and localize the process before this event occurs *hematogenous dissemination* may take place by rupture of a tuberculous focus into the lymphatics or veins with a resultant *bacteremia* Tubercle bacilli are carried to all organs of the body though most of them enter the venous return to the right side of the heart and hence are seeded back into the lungs

The outcome and progression of the dissemination depend upon the size of the seedin and the resistance of the tissues of the host If the seeding is small and resistance adequate the microscopic tubercles in the lungs and other organs may heal completely lled

of specific agglutinins In the typhoidal variety blood and stool cultures are frequently positive In the food poisoning variety of infection blood cultures are rarely if ever positive whereas stool cultures are only positive in the more severely ill patients and then most often when the specimen is obtained soon after the onset of symptoms

Agglutinins develop in the second and third week of the disease in the typhoidal variety The significance of H and O agglutinins and the occurrence of cross reactions are included in the discussion of the subject under typhoid fever (p 233) The acute gastro enteritis variety rarely results in a significant rise in antibodies If agglutinins appear at all their recognition occurs too late to be of diagnostic help

PROGNOSIS

The food poisoning type of Salmonella infection ordinarily has a negligible death rate The mortality of the typhoidal infections is generally from 2 to 5 per cent varying with age and clinical severity

TREATMENT

The treatment of the typhoidal type of infection is identical with that of true typhoid fever (p 236) The treatment of botulism is considered in a subsequent section (p 313)

PREVENTION

The safeguarding of food and water supplies has reduced the prevalence of Salmonella infections though to a lesser extent than that of typhoid fever Animal carriers and natural infection of food sources hinder the conquest of many types of Salmonella infection The prevention of food contamination in canning and preserving is considered elsewhere (p 313)

Active immunization is possible Paratyphoid A and B may be included with typhoid vaccine

BACILLARY DYSENTERY

Bacillary dysentery is an acute infectious disease caused by various members of the group of *Shigellae* It is characterized clinically by an acute diarrhea accompanied by fever vomiting abdominal pain and tenesmus and the passage of stools containing blood mucus and pus

Bacteriology —The common organisms in the group of Shigellae include the Shiga Schmitz (*B ambiguum*) Flexner Sonne Newcastle and dispar varieties

The dysentery organisms are gram negative rods morphologically indistinguishable from the Salmonellae and the nonpathogenic coli They are non motile and do not usually produce gas when they ferment various sugars

The bacteriologic and biochemical aspects of the subject and the technics of stool culturing are considered in the discussion of *E typhosa* (p 225)

Epidemiology —Bacillary dysentery occurs throughout the world Epidemics are more common in tropical countries rural communities and camps where community sanitation is adequate Although outbursts of bacillary dysentery may be water or milk borne the usual method of transmission is by infection of food The fly has been incriminated as the vector which frequently carries the organism from feces to food As in typhoid the chronic carrier may often play the same role All age groups are affected but young infants seem particularly susceptible to bacillary dysentery The disease is most prevalent in summer but winter epidemics are not uncommon

In the United States the disease is endemic and from time to time small localized outbreaks appear It is most common in asylums mental hospitals nursing homes prisons and

the endogenous theory of pulmonary tuberculosis which holds that the adult type of disease is a reactivation of earlier lesions In contrast to this view the *reinfection* theory states in essence that adult tuberculosis is due to exogenous reinfection in a person whose tissues have been previously sensitized by a primary type of infection There is every evidence that reinfection sometimes does occur and authorities differ chiefly over the question of whether endogenous reactivation or exogenous reinfection is more common in the adult

Immunity—There is no evidence that *humoral antibodies* play any significant role in the immunity to tuberculosis Rather do the data point to a *tissue immunity* which undoubtedly resides in the *macrophages* The sera of highly immunized animals have no bactericidal action on tubercle bacilli in vitro Agglutinins occasionally may be demonstrated in the serum of tuberculous patients but never consistently in high titer

The effects on tuberculosis of *natural immunity* race and heredity have been mentioned earlier *Acquired immunity* in tuberculosis was first demonstrated by Koch who showed that if a normal guinea pig is injected subcutaneously with tubercle bacilli no gross changes occur at the site of injection for a week or more At the end of this time a papule appears which ulcerates At the same time the regional lymph nodes enlarge and eventually the animal dies of generalized tuberculosis On the other hand if a tuberculous guinea pig is similarly injected there is an immediate intense inflammatory reaction at the site of injection followed by necrosis of the skin and eventual healing the regional lymph nodes are not involved and dissemination of tubercle bacilli does not occur The tuberculous animal or patient is hypersensitive to tubercle bacilli or its products and reacts with an immediate inflammation which serves to block the spread of the organisms In so doing local death of tissue may occur and this apparently is the price the allergic animal pays for localization of the infection

There has been much discussion of the harmful or beneficial effects of allergy in tuberculosis *Rich is of the opinion that allergy is not the same as immunity* He maintains that they are separate phenomena and can be dissociated by desensitization It appears that allergy in tuberculosis is closely associated with the development of tissue resistance and seems on the whole to be a beneficial and protective reaction

CLINICAL MANIFESTATIONS

The present section deals with the clinical manifestations of the primary and disseminative phases of tuberculosis The localizing symptoms due to end organ tuberculosis are considered later under the several headings such as pulmonary intestinal lymphatic genital, urinary

PRIMARY INFECTION

The primary infection produces no localizing symptoms or signs yet close observation of the patient may disclose suggestive constitutional and systemic manifestations

Subjective and Objective Findings in Subclinical Tuberculosis—The subjective symptomatology is vague and ill defined The patient seems *indolent* and *fatigues* more easily than usual There is a complaint of *lack of pep* *disinterestedness* and *apathy* There may be *loss of appetite* and *general querulousness* It is noted that the patient seems not to look well The color is bad There are rings and circles under the eyes The mother particularly asserts that the child is just 'not right The temperature record (p 3484) reveals a *low grade* or *relative pyrexia* in that the diurnal variations exceed 1° F There may be a slight *relative tachycardia* In the growing child the gain in weight falls below the expected level or ceases In the adult there may be an actual *decrease in weight*

While primary tuberculosis may occur at any age it is most common in children and produces considerable morbidity and mortality before the age of two years In the young erythema nodosum is an occasional manifestation and expiratory stridors are heard when enlarged nodes compress a bronchus prior to atelectasis

infants rectal prolapse is not uncommon and vomiting and signs of dehydration also occur Meningismus may be an early symptom

The usual *course* of acute dysentery of moderate severity is a week to ten days The fever and constitutional symptoms subside before the consistency of the stools returns to normal

FULMINATING INFECTIONS

Fulminating dysentery simulating cholera with a profuse outpouring of fluid from the bowel and the rapid development of shock is described in the Orient These infections are due to infection with the *Shiga* organism It is probable that the overwhelming toxemia is due to the toxins elaborated by the organism

DIAGNOSIS

In sporadic cases the general practitioner can achieve no more than a suspicion of the presence of bacillary dysentery At best he carefully obtains a culture from the stool or a rectal swab and turns the specimen over to the experienced bacteriologist for *culturing* and *identification* In the presence of an epidemic the diagnosis is naturally made with greater facility and physicians in tropical countries whose experience is large believe that they can make an etiologic diagnosis by inspection of the stool which contains mucous shreds large numbers of polymorphonuclear leukocytes and red blood cells Certainly in the United States where the milder manifestations of bacillary dysentery are most commonly seen these clinical criteria would not hold and many surprises might be expected to result from the findings of the laboratory See *Differential Diagnosis of Diarrhea* pp 1840 2782

Stool Cultures —The definitive diagnosis of bacillary dysentery depends most often on the cultural isolation and identification of the organisms from the stool Since most dysentery organisms die quickly once they are excreted the stool must be cultured within an hour of passage If this is not possible the stool is diluted with two parts of a preservative consisting of 30 per cent glycerin in saline solution Even with these aids the organism may fail to grow out in the culture so that it is necessary to make repeated examinations in suspicious instances A higher percentage of positive results is obtained when cultures are secured by the rectal swab method rather than direct plating of the stool itself The *Sonne* variety of Shigella is more easily cultured than the *Shiga*

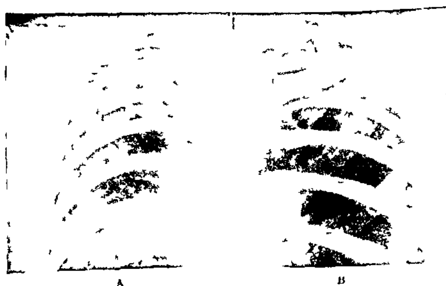
Blood cultures are invariably sterile but the organisms are occasionally present in the *urine* Unlike typhoid fever the stool culture is positive at the beginning of the disease

Agglutinins —Agglutinins develop by the end of the first week or the beginning of the second week of infection Since the disease is usually subsiding by that time the serologic tests have little practical diagnostic significance Furthermore the titer of the agglutinins is rarely high and as some normal individuals exhibit titers as high as those of patients with the disease chief reliance must be placed on the stool cultures

Hemogram —There is no specific change in the blood count A *leukocytosis* of moderate degree is usually present in the acute attack *Anemia* develops if the disease is protracted

A B

Fig 32 —*A* Asymptomatic stage of tuberculosis August 29 1939 Bilateral hilar thickenings more marked on right and extending out towards periphery Reticulation and slight diminution of radio translucency of left upper lobe and apex *B* Same patient April 3 1941 Clinical tuberculosis with smudge infiltration in left infraclavicular and apical regions replacing reticulations of film taken 20 months previously



A B

Fig 33 —*A* Minimum soft infiltration with reticulation in right apical region *B* Minimum infiltration with reticulation infraclavicularly on left

SPECIFIC SERUM THERAPY

It is the current view of the United States Navy that polyvalent *Anti dysenteric Serum* (*N.N.R.*) is of no value and hence is not recommended. The *monovalent Shiga serum* is suggested but only after there has been confirmation of the presence of the specific organism. A dose of at least 40 to 80 cc (10 to 20 fluid drams) daily is recommended until the symptoms subside. The preparation may be given intramuscularly without dilution. If given intravenously it is made up to 500 cc with normal saline and injected by the method of the slow intravenous drip (p 87).

TREATMENT WITH THE ANTI INFECTIVE AGENTS

While *penicillin* is of no value in the treatment of bacillary dysentery there are indications that the condition may be alleviated by both the *soluble* and *insoluble sulfonamides*. *Sulfadiazine* has proven effectual against *S flexneri*, *S shiga*, *S sonnei* and *S newcastle* when given in an initial dose of 3 gm (45 grains) followed by 1 gm (15 grains) every four hours by night and day. If improvement occurs in three days or less the dose may be reduced to 1 gm (15 grains) until the stools have been normal ninety six hours. If there is no improvement the use of the insoluble sulfonamides such as *sulfaguanidine*, *sulfasuxidine* and *sulfathalidine* is advised. These drugs are poorly absorbed and the greater part of the oral dose remains in the intestinal tract where it is capable of acting locally on the intestinal mucous membrane and the organism contained within the lumen (p 101).

The initial dose of sulfaguanidine or sulfasuxidine is 0.1 gm per kilogram of body weight. The maintenance dose is 0.05 gm per kilo every four hours until the number of the stools has been reduced to four or less a day. At this time the dosage may be reduced to 0.1 gm per kilo every six or eight hours and maintained at this level until the number and appearance of the stools have been normal for at least four or five days. Relapses may be encountered if drug therapy is prematurely discontinued. The practitioner should not be alarmed at the seemingly large size of the initial and maintenance doses. The adult of average size requires according to the above calculations 6 to 7 gm (90 to 105 grains) as the initial dose and 3 to 4 gm (45 to 60 grains) as the maintenance amount at four hour intervals.

Streptomycin (p 104) has proven as disappointing in the specific treatment of the bacillary dysenteries as it appears to be in the management of typhoidal fevers (p 236). As in the latter disturbances combination therapy using oral and parenteral dosages were employed. A daily oral unitage of 500 000 to four million units was given in four or five divided doses. Similar amounts were administered by supplementary intramuscular injection using at least 250 000 units in physiologic saline every six hours for four doses. So far as is presently known streptomycin therapy may be combined with the administration of the sulfonamides particularly in severe infections. Antibiotic therapy does not interfere with the parenteral administration of fluids nor does it preclude the use of serum in those patients who fail to respond satisfactorily within thirty six to sixty hours.

See *Differential Diagnosis of Commoner Febrile Skeletal Disorders* (p 192)

Tuberculous Meningitis—Tuberculous meningitis is a common termination for miliary tuberculosis particularly in children Often the first positive indication of the disease is the demonstration of the *choroid tubercle* visible by opthalmoscopy (p 1603)

The *prodromal symptoms* of tuberculous meningitis are essentially those of the typhoidal form Later, *persistent vomiting* and *headache* arouse the suspicion of the practitioner and he makes note of *meningeal* and *neurological manifestations* The vomiting bears no relation to meals and the headache is not relieved by the ordinary simple measures of treatment The child appears more prostrated and stuporous than the febrile elevation would suggest The hours of sleep are increased and it is more difficult to awaken the youngster There is a certain amount of *photophobia* and isolated and transitory periods of *delirium* At this time it should be possible to demonstrate sufficient signs of *meningeal irritation* to warrant the performance of a lumbar puncture The *neck is somewhat stiff* or it may be possible to bring out *Kernig* or *Brudzinski signs* (p 3572) There are occasional and transitory evidences of motor weakness such as *nystagmus* and *strabismus* or there may be *muscle contractions* with tonic or clonic movements Finally, in the fullblown syndrome there are the more obvious signs of *meningitis* often with *convulsions* (p 1519) Infants reveal a tenseness of the *fontanelle* with bulging See *Differential Diagnosis of Nonsuppurative Encephalomyelomeningitides*

The definitive diagnosis of tuberculous meningitis is made by painstaking search for the organism in the *fibrin clot* that forms after *spinal fluid* has stood for twenty four hours Presumptive evidence of the infection is afforded by the associated data which include clear fluid containing a large number of lymphocytes and a lower chloride concentration

While the course of tuberculous meningitis has always been unfavorable streptomycin (p 267) holds out some promise for amelioration

TUBERCULIDS

The skin tuberculids include the tubercular chancre tuberculosis verrucosa cutis scrofuloderma tuberculous ulcers lupus vulgaris lichen scrofulosus the papulonecrotic tuberculid lupus miliaris disseminatus faciei the rosacea like tuberculid of Lewandowsky erythema induratum and sarcoidosis (p 3271)

ORGAN TUBERCULOSIS

See *Pulmonary Tuberculosis* (p 2200) *Renal Tuberculosis* (p 2347) *Intestinal Tuberculosis* (p 1860) *Laryngeal Tuberculosis* (p 2161) *Ocular Tuberculosis* (p 1603)

TUBERCULIN TESTS

The tuberculin test dependent upon allergic sensitivity to fractions of the tubercle bacillus is a useful diagnostic test Of the many preparations Old Tuberculin (O T) USP as made originally by Koch and PPD (purified protein derivative) NNR are in common use PPD is 100 to 200 times more potent than OT it is stable and purified and has many advantages over the older preparation

found the descriptions of colon bacillus cystitis pyelitis and pyelonephritis puerperal infections appear in the chapters on the Female Reproductive Organs and cholecystitis and peritonitis are included with the material on the Digestive System

Bacteremia —Colon bacillus bacteremia is an uncommon condition which usually arises from instrumentation of the urinary tract and infections of the gallbladder kidneys prostate or peritoneum

The suspicion of a colon bacillus bacteremia arises when following instrumentation or during the course of a localized infection the patient develops an abrupt *rise in temperature* with severe *chills* Usually the invasion of the blood stream is accompanied by a tachycardia and a leukocytosis but sometimes there is a leukopenia and a bradycardia simulating the conditions seen in typhoid fever Fulminating colon bacillus bacteremia occasionally arises with a rapid onset of fever and drowsiness lapsing into coma This complication is most frequently observed in diabetic women with pyelitis or pyelonephritis The clinical syndrome suggests a diabetic coma but the presence of a high fever and the absence of dehydration point to infection rather than acidosis

A definitive diagnosis of colon bacillus bacteremia is possible only through blood cultures The organism grows on all common laboratory media It requires differentiation (p 226) from other gram negative bacilli

TREATMENT

The treatment of the localized colon bacillus infection is detailed in the several chapters The present section deals only with systemic invasion

Prevention —Colon bacillus bacteremia is a serious condition that carries a grave prognosis Preventive measures include the prompt recognition and thorough control of local processes and the avoidance of instrumentation through inflamed tissue Should it be necessary to pass catheters cystoscopes or sounds through an infected area the patient should be protected by *prophylactic antibiotic therapy* using sulfonamide (p 88) or streptomycin (p 104)

Antibiotic Therapy —Antibiotic therapy of colon bacillus infections can be accomplished with sulfonamides and/or streptomycin Streptomycin gives greater promise of remarkably specific potency in bacteremias biliary infections urinary sepsis and peritonitis produced by gram negative organisms In the treatment of these disturbances streptomycin is given intramuscularly using 500 000 units eight times daily Oral do es are not absorbed and remain within the intestinal lumen Treatment should be continued for a minimum of seven and preferably ten to fourteen days in order to prevent relapse since organism resistance frequently develops

Surgery —Where indicated *surgical therapy* is utilized The *indicated* operative procedures may require the removal of gallbladder or appendix and the drainage of peritoneal collections of pus or renal abscesses Technical procedures are preceded and followed by chemotherapy

ASIATIC CHOLERA

From time to time and as recently as the latter part of the 19th century epidemics of cholera have raged throughout the world At present the disease is endemic in Asia particularly in India where large numbers of infections occur each year

Interpretations—The positive and negative tuberculin tests require careful interpretation since either may be most misleading A *positive* tuberculin test means that the patient is allergic or hypersensitive to tuberculin and has tuberculous tissue in the body It does not necessarily indicate present activity since the infection may be old walled off calcified completely latent or active

The negative test also may give erroneous information Thus in the tuberculous patient, a negative test may be found early in the infection during an intercurrent disease such as measles and in the terminal stages of an advanced tuberculosis In the absence of these conditions however it indicates that the patient is neither allergic nor hypersensitive to tuberculin and does not possess tuberculous tissue in his body



Fig 85—The patch tuberculin reaction *

Diagnosis

The diagnostic problem in tuberculosis is complicated by the frequency of inactive lesions in association with other clinical conditions The practitioner must not only determine the presence of the disease but must also estimate its degree of activity and its relationship to the prevailing symptomatology

Definitive Diagnosis

The definitive diagnosis of tuberculosis is made only by the demonstration of the presence of the organism when there is organ involvement Tubercle bacilli cannot be grown from the blood stream except under extraordinary circumstances cultural growth is difficult and, in all but the exceptional circumstance the bacilli are identified through microscopical examination of stained smears (p 52) of sputum urine spinal fluid gastric content feces or peritoneal fluid In the majority of instances the *specimen must be concentrated* before the smear is made In the remaining instances in which the condition is recognized the diagnosis is made through

* Kolmer and Tuft

subcutaneously every six months as long as there is danger of infection by the cholera vibrio The cholera vaccine may be given concurrently with the typhoid suspension No severe reactions are usually noted though there may be local pain at the site of injection The value of vaccine has been conclusively established though the immunity is only relative and of short duration lasting from six to twelve months

Antibiotic Therapy—Combination therapy using intravenous saline and plasma with oral doses of sulfadiazine or the intravenous introduction of sodium sulfadiazine has been signally successful in the active treatment of Asiatic cholera The initial dose of the sulfonamide should be no less than 5 gm (75 grains) with maintenance doses of 0.5 to 1 0 gm (7½ to 15 grains) every three or four hours thereafter Equally promising is the prospect of the use of combined oral and parenteral streptomycin (p 104) as described in the treatment of typhoid fever (p 236)

Symptomatic Treatment—The most important feature of active treatment is the replacement of lost fluid by parenteral injections of large amounts of saline given slowly by subcutaneous clysis (p 3771) or intravenous drip (p 3775) Plasma infusions and blood transfusions to restore blood volume together with liberal fluid intakes of salt water and tea appear to produce results almost as striking as those obtained with the antibiotics

the common cold pneumococcus pneumonia syphilis acute appendicitis peptic ulcer carcinomatosis and the remaining common afflictions of human tissue It requires mature clinical acumen to decide whether the presenting problem is due to the tuberculous infection or whether it just happens to occur in a tuberculous individual and bears no relationship to the pristine infection

Course and Prognosis

The course of tuberculous infections is characterized by its long duration Simultaneously there exists the stubborn tendency of the bacillus to thrive and of the tissues to heal Of those of us who suffer the primary infection the overwhelming percentage seemingly manifest no ill effects from the disease In contrast to this the immediate outlook in disseminative tuberculosis is grave and that of the meningeal variety ominous though the practitioner will see survivals in both the typhoidal and the pulmonary varieties despite a period of seeming hopelessness

The outlook in pulmonary tuberculosis with use of modern therapy is a source of constant rejoicing to the practitioner who may now look on the well known euphoria of the tuberculous as an actuality rather than a myth The surgeons have brightened the prognosis of tuberculosis in unilateral renal involvements (p 2347) and in the procedures aimed at localized pulmonary disease (p 2208)

Treatment

The present section deals with preventive and curative methods of treatment for tuberculosis The local treatment of end organ tuberculosis as in the lungs or kidneys is to be found in the several chapters

Specific Treatment

The specific treatment of tuberculosis despite titanic efforts on the part of experimenters and clinicians has thus far been a disappointing chapter in the history of medicine The preparations that have been tried include vaccines tuberculins serums and drugs

Vaccine Therapy —Vaccine therapy using dead organisms has been unsuccessful After tragic consequences in Europe the Calmette experiment of injecting attenuated living tubercle bacilli as BCG vaccine is being reinvestigated in America with suggestively promising results Also a trial of intracutaneous injections of vole bacillus prior to infection of guinea pigs with virulent human organisms appears to give protection

Tuberculin —There is no theoretical reason for tuberculin injections to do anything other than desensitize the patient to the protein of the tubercle bacillus To those who regard tuberculin sensitivity as a beneficial defensive reaction therapeutic desensitization would seem contraindicated Certainly it has been the experience of the clinician that tuberculin injections accomplish nothing of specific value to the patient If improvement is noted simultaneously with the injections it is most likely the spontaneous course of the disease rather than a specific curative effect

The most popular use of tuberculin has been in the field of ophthalmology With few exceptions experienced specialists are agreed that observed benefits are probably in the nature of nonspecific therapy resulting from the constitutional reactions to the injected protein

Serum Therapy —*Humoral antibodies* cannot be demonstrated in tuber

Epidemiology—Man can be infected only with human or bovine strains of tubercle bacilli *Human tubercle bacilli* are transferred from person to person in sputum or saliva droplets by contamination of household objects or by inhalation of dust mixed with infected sputum Inhalation is therefore the chief route of entrance of tubercle bacilli into the body and accounts for the fact that the primary lesion of the human strain is almost always in the lungs

Infection with the *bovine strain* results from the ingestion of raw milk obtained from tuberculous cows This was formerly a common source of human tuberculosis but the successful control and virtual elimination of tuberculosis in cattle have rendered bovine infection an uncommon incident in the United States In countries where raw milk is still consumed by the majority of people bovine tuberculosis accounts for a large number of human cases of tuberculosis The universal practice of pasteurization of milk could eliminate this type of disease The enteral portal of entry for bovine strains explains the frequency with which the organisms produce mesenteric lesions particularly in the young

All persons are susceptible to tuberculosis and will contract the disease if subjected to massive infection Certain races are seemingly resistant while others appear extremely susceptible



Fig 26—The pathology of tuberculosis Caseous primary subpleural lesions in upper and lower lobes of child's lung with secondary caseous bronchial lymph nodes

Certain occupations particularly the dusty trades have an increased hazard Certainly the level of general nutrition overcrowding and poor living conditions are closely related to the incidence of tuberculosis and to a certain extent the decreasing mortality from tuberculosis is probably the result of the improvement in housing that has been accomplished for the masses of the people in this country during the past thirty years

Tuberculin testing of large groups of people has shown that *inapparent infections are extremely common* At one time it was believed that by the time adult life was reached almost everyone had been infected with the tubercle bacillus The great majority of the infections of course were entirely latent and became manifest only as calcified nodules or apical lung fibrosis In recent years however it has become evident that this tenet no longer holds Due to the prompt detection and isolation of infectious cases the opportunity for chance infection among the mass of people has been greatly reduced and there are areas in the United States where more than 50 per cent of persons reach adult life without having developed a positive tuberculin reaction

tarium stays in his own locality or seeks a more favorable climate he must remain in bed during and following the periods of activity Bed rest means exactly what the words imply Bed pan and urinal are employed The in fected individual remains recumbent for twenty four hours in the day

Rest at Home—Home care for the tuberculous has emotional and psychological advantages It involves heroic sacrifice on the part of the housewife and some improvisations in nursing and medical care In gen eral the practitioner should advocate home care only under the following circumstances

1 The lesion must be relatively inactive
2 The danger of spread of infection to other members of the household particularly younger children is minimal
3 The mother or wife is able to stay in constant attendance
4 The attendant is sufficiently intelligent to read a thermometer and count a pulse rate and sufficiently cooperative to carry out all orders without variation
5 The home must provide fresh air sunshine clean and well cooked food and quiet
6 The patient must be able to occupy a room alone preferably with a bath
7 The attendant must be able to follow out preventive treatment *relative to the disposition* of sputum care of dishes silver and glassware

Sanitarium Care—Admission to an institution or a sanitarium is man datory under the following circumstances

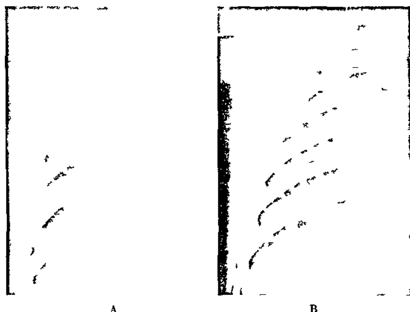
1 The lesion is active so that constant medical care is required for management and treatment
2 The home is one in which the patient cannot get quiet fresh air or intelligent nursing care
3 The economic status is such that the necessary food drugs and medical attention are beyond the budgetary limits
4 Home care has been unsuccessful

Between these extremes the decision as to home or sanitarium care is an individual matter In settling this point the physician summarizes the pros and cons the patient and family ultimately must reach their own conclusion

Climatotherapy—The wisdom and advisability of climatotherapy (p 3761) are debated in most tuberculous infections The following statements are justified

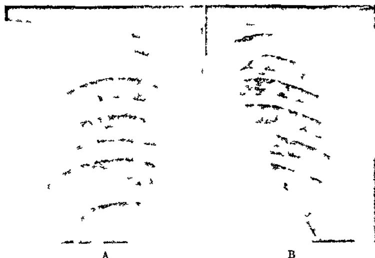
1 Climatotherapy has no specific effect on the course of tuberculosis
2 Certain of the demonstrable advantages of climate can be obtained in the home by air conditioning machines (p 3763) and artificial sources of ultraviolet radiation (p 3793)
3 The expense of climatotherapy is great due to the cost of transportation and necessity of finding a new abode
4 Climatotherapy requires either the separation of the patient from his family which is often most unfortunate or the transplantation of the family to the more equable climate which may mean the sacrifice of many for the one Nevertheless there is no gainsaying the fact that it is pleasanter to enjoy the balmy air and blue skies of the desert states than to gaze at four walls and grey skies But there must also be recognition of the fact that many people cling to the attitude that be it ever so humble there is no place like home

Th Primary Complex—Inhaled tubercle bacilli reach the lungs and set up a *primary lesion* wh ch occurs most often in the right lung Contrary to the general impression it is



A B

Fig 28—*A* Pr mary complex of r ght lung in an infant on Nov 25 1936 *B* Same infant Dec 6 1939 Healing of parenchymal le ions with calcification in regions of hilum llustrating bipolar p ary compl x and formation of Ghon tubercles Observe sharp delineat on of calcified shadows



A B

Fig 29—*A* Soft ri ht inf aclavi ular minimum infiltration Note fuzziness and haziness as comp ed with Fig 28 *B* *B* Soft left nfracla icular minimum infiltration with fan l ke reticulations sp eading out from hilum

infrequently apical and most often infraclavicular It varies in s ze according to the numbers of the infecting organisms their virulence and the immunity of the host See Figs 26 27 28 29

should be warned that the feeling of warmth that follows the ingestion of the alcoholic beverage is not an indication of fever

Care of the Mouth and Bowels—The bed patient needs particular care relative to oral and bowel hygiene The teeth are to be brushed after each meal The local dentist is encouraged to make a survey every few months during the period of bed rest Dental floss is used to remove gross particles from between the teeth and the mouth should be rinsed regularly

The care of the bowels is often an annoying problem Cathartic drugs should be avoided but *mineral oil* may be taken at night to soften the stool If there is not a successful evacuation immediately after breakfast a glycerin suppository is inserted to clear out the rectal ampulla Should this device fail a small enema is advisable since constipation may be a cause of anorexia

Fresh Air—It was only a generation ago that the tuberculous patient was shielded from contact with fresh air due to the fear of draughts and chilling The world is indebted again to Trudeau who founded his sanitarium in the Adirondack mountain region in the State of New York where he clearly demonstrated the virtues of fresh air treatment There can be no question in the mind of the modern physician that the patient eats better sleeps better and feels better when he is removed from the hothouse atmosphere of a room filled with stale warm enervating air and is transferred to the outdoors

The practitioner must occasionally remind patients that the advocates of fresh air treatment do not intend that the tuberculous individual should be chilled On the contrary he is well bundled up the head is protected by a cap sun glasses are worn and a scarf is thrown about the neck If the reaction to fresh air is unfavorable and produces shivering or slight cyanosis the patient is transferred indoors and is not made to suffer discomfort nor is there any necessity for going to the extreme of remaining outdoors if the rain beats in and the atmosphere is moist and clammy

Heliotherapy—Exposure to sunlight or the artificial ultraviolet ray has possibilities both for good and evil in tuberculosis The artificial sources have the advantage over the natural sunlight in that they are more readily controlled as to dosage Hence their use is preferred except under the most unusual circumstances

In using this modality the practitioner should ascertain the reliability of the apparatus by utilizing only a model that has the stamp of approval of the Council on Physical Medicine of the American Medical Association He should follow the manufacturer s directions to the smallest detail observing the effects on his individual patient with meticulous care

It is wise to employ heliotherapy in a probatory fashion The patient is exposed to the ray under measured conditions as to length of time and *distance from the source of the emanation The results are observed* with relation to subjective symptomatology pulse rate and temperature record The dosage is stepped up judiciously if the reaction is neutral or favorable but it is discontinued immediately there are evidences of intolerance

Drugs—Drugs are a mere accessory in the treatment of tuberculosis unless given for symptomatic relief The bed patient is often benefited by the use of sedatives and hypnotics *Phenobarbital* in doses of 16 mg (¼ grain) often helps relax the patient throughout the day The prescription

off and latent If the seeding is massive and resistance is low *acute miliary tuberculosis* (p 61) results Various types of *protracted miliary chronic hematogenous* l s ons in the lungs and other organs may result from repeated dissemination of bacilli Clinical symptoms may or may not be associated with this stage of the disease *Tuberculous meningitis* the ocular and cutaneous tuberculids probably occur in this phase and *tuberculous pleurisy with effus on* (p 2 21) which is an allerg c react on to tubercles on the pleural surface is also a result of the dissemination of bacilli

Chron c Organ Tuberculosis—The third phase of the evolution of tuberculosis is the development and progression of *chronic tuberculosis of the organs* If resistance is high and the dosage small the disseminated les ons may heal completely or may remain walled-off and latent Then months or yea s later they may become active and sl ly or rap lly progre What factor upsets the balance between host and parasite is not always clear Malnutrit or

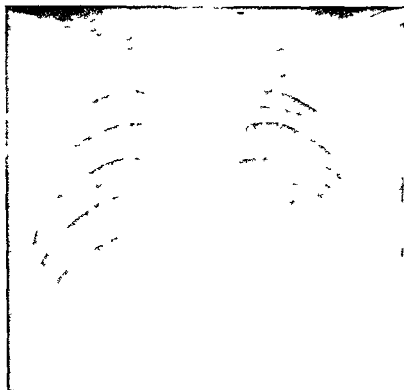


Fig 31—Film taken Jun 1 1940 of same pat ent as Fig 30 howing d seminat n and i lary typ of tuberculosis Death occurred July 29 1940 Co firmatory autopsy was p r form d

intercurrent illness psychogenic disturbance and p egnancy may lower tissue resi tan e to th po t wh e the ba ter a a a n become a t ve The re ult is the de elopment of cl nical tube culos s of the kidneys gen tal tract bones or what ver other o gans may have been in ol e l in the or ginal dis m nat on of the ba illi

Chro c or an tube culosis is chiefly found in the *lungs* s n e it is here that the heav est dissem nat on occurs du ng the second sta e The result is *chronic pulmona y tuberculosis* (p 200) Any a i ty of low o rapid p og essio with ca ity formati n bronchogenic spr d or fibrosis may occur Here ag n the type and progres on of the lesion depend to a la g extent upon the l vel of tissue res tance The patholo y and clinical cou se f pul monary d other types of hroni tube culosis are ons d d in other sections (p 199)

Endogen us" nd Reinf tion Hypothese of the Pathogenes of Tube culosis—The forego ng hypothes s supported by a mass of clinical and pathological evidence constitutes

Clinical Manifestations

Leprosy manifests itself by cutaneous and neural disturbances Many patients display both types of lesions

CUTANEOUS OR NODULAR LEPROSY

Cutaneous or nodular leprosy is characterized by the presence of multiple firm smooth, glazed *nodules* These may be brown or tan in color and have a predilection for the cheeks nose forehead and skin They may also be scattered widely over the trunk and extremities On the face the

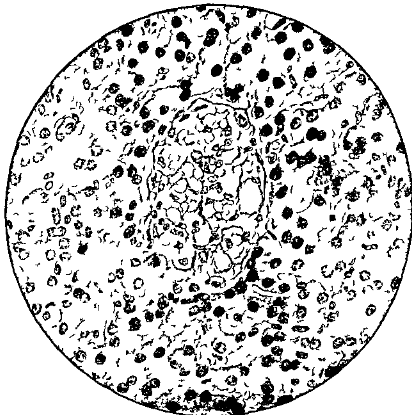


Fig 36—Lepra cells in the liver

marked infiltration leads to the so called '*leonine facies* which is often accompanied by *alopecia of the eyebrows* (Fig 37)

The nodular lesions are *anesthetic* and in the course of time they *ulcerate* and produce disfiguring destruction of tissue The inflammation may involve the mucous membranes of the nose and the resultant ulceration completely destroys this organ

NEURAL OR ANESTHETIC LEPROSY

Neural leprosy results in loss of nerve function The branches frequently affected are the *ulnar* and *peroneal* though others also may become dis

* MacCallum, Textbook of Pathology

Laboratory Data—At this time the *tuberculin test* becomes positive and if a negative test had been previously recorded the change is of particular significance A *chest film* may reveal the small infiltration that is more often infraclavicular in its position than apical The radiographic findings are of greater significance if a previous film is available for comparison There may be a *slight anemia* and a *slight increase in the sedimentation rate*

Diagnosis—The diagnosis of the primary infection rests on the high index of suspicion that exists in the mind of the astute practitioner Often his curiosity is aroused by the tuberculin test or a family history of tuberculosis At the time of the primary infection a demonstration of tubercle bacilli is unlikely Concentrated sputum specimens are examined With children who cannot spit a search for the organism is conducted in concentrated fasting gastric content or stool

Roentgenologic examination is imperative in primary tuberculosis since diagnosis otherwise may be well nigh impossible The pulmonary focus may be seen (Fig 28) as a hazy area of infiltration in any portion of the lung but it is most often infraclavicular and on the right side although it may left sided (Fig 33 *B* p *260*) apical or basal Lymph node enlargement may be noted in the hilar region on one side or it may be traced up the side of the trachea to paratracheal groups Atelectasis or local emphysema may occur when bronchial obstruction is present Several years after the primary infection both poles of the primary complex may be represented by calcareous deposits The association of progressive roentgen changes with a change to positivity in a previously negative tuberculin reaction furnishes overwhelming cumulative evidence

The differential diagnosis is most difficult and may require long observation and the exercise of a sensitive judgment The conditions which simulate subclinical tuberculosis range from conduct and personality disorders to chronic infections in the accessory *na al sinuses* (p 2131) *rheumatic fever* (p 186) or *brucellosis* (p 314) There are no positive methods of distinguishing these conditions other than by prolonged observation of the evolution and involution of the clinical picture

Prognosis and Complications—The primary infection usually heals without overt clinical signs When systemic signs are present a *happy* outcome is to be expected if with bed rest there is a fairly prompt subsidence of activity Ominous signs include prolonged and high fever extensive pulmonary involvement with necrosis bronchogenic dissemination massive lymph node enlargement and signs of bronchial compression During the phase of primary infection hematogenous dissemination is a frequent occurrence This may be the forerunner of end organ tuberculosis in any part of the body or of miliary tuberculosis

Treatment—The management of the primary infection involves the exercise of the general principles of treatment elsewhere delineated (p 267) The practitioner is wise if he errs on the side of conservatism and overtreats his patient rather than risk an underestimation of the condition

PREPHTHISICAL TUBERCULOSIS

Because of changes in the immunology of tuberculosis adult prephthisical lesions are increasingly recognized The criteria for diagnosis include

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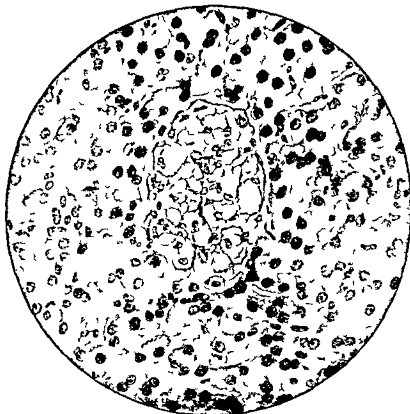


Fig 36—Lepra cells in the liver *

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Neural leprosy results in loss of nerve function The branches frequently affected are the *ulnar* and *peroneal* though others also may become dis

* MacCallum, Textbook of Pathology

recently acquired tuberculin sensitiveness increased x ray reticulation (Figs 32 33) that is widely scattered or restricted to one area in the upper lung fields (Dunham s Fan) a recent pleurisy with effusion persistent homogenous infiltration (round focus) or a cluster of small inter con nected foci (smudge focus)

Treatment —Prephthisical tuberculosis requires rest treatment (p 267) in order to prevent the development of classical chronic pulmonary tuber culosis

MILIARY TUBERCULOSIS

Miliary tuberculosis is brought about by dissemination through the body of large numbers of virulent tubercle bacilli There may be single or repeated seedings Manifestations may be clinically apparent as a gen eralized typhoidal a pulmonary or meningitic form Miliary tuberculosis is most common before the age of three and especially in the first year when bacilli are disseminated from the fresh primary complex Peaks of incidence occur also at puberty and later in life as an agonal manifestation in the debilitated

Typhoidal Form of Miliary Tuberculosis —The typhoidal form of miliary tuberculosis is a baffling syndrome that is usually suspected when all diagnostic tests for other demonstrable organisms have been exhausted

The *onset* of the disease is usually gradual with fever anorexia head ache prostration or nosebleed As the symptoms continue respirations become disproportionately increased with accompanying *dyspnea or cyan osis* and the *spleen may be enlarged* The entire syndrome is characterized by an absence of localizing physical findings and by normal laboratory data The tuberculin test is usually but not invariably positive

The *blood counts* are very little altered *Blood culture* is sterile *Stool and urine cultures* reveal only the usual organisms The *agglutination reac tions* particularly for typhoid and the Salmonellae are normal or mislead ing See *Differential Diagnosis of Cryptogenic Fevers* (p 26)

Occasionally the miliary process continues without localization and the diagnosis is made only at autopsy More often however the diagnosis reveals itself by the demonstration of pulmonary meningeal or choroidal tubercles

Pulmonary Form of Miliary Tuberculosis —The pulmonary form of miliary tuberculosis is suspected clinically when in a febrile illness the attention of the practitioner is drawn to the lungs by a relative disproportion between the *rapidity of respiration* and the height of the temperature or by con tinuing *dyspnea* and *cyanosis* With the attention focused on the lungs repeated examinations may reveal scattered areas of dullness and an occa sional subcrepitant rale If it is possible to obtain a *radiograph* at this time an extensive infiltration is visible out of all proportion to the phys ical signs *Bacilli* may be demonstrable in concentrated sputum gastric contents or feces

The course of the disease is variable In progressive examples air hunger increases the pulmonary infiltrations extend and the patient even tually dies within one to three months On rarer occasions the process subsides or passes over into one of the chronic forms of pulmonary tuber culosis (p 2199)

the extremities but may involve the *neck and trunk*. The lesions are brown or tan colored round small and *hyperesthetic* in the early stages. Later they enlarge and become atrophic, *depigmented and anesthetic*.

SARCOIDAL LEPROSY

An infrequent variety of leprosy is the sarcoidal type which consists of the development of *elevated papules* and *plaques* (Fig 39). These are skin colored and may be pigmented or depigmented. These lesions resemble *sarcoidosis* (p 3271) and the pathology is often indistinguishable although the microscopic diagnosis is afforded by the demonstration of the lepra bacilli.

DIAGNOSIS

In regions where leprosy is endemic the manifestations of the disease are *easily* recognized. However in a community where the disease is



Fig 39.—Patient with mixed leprosy of 19 years duration before and after one year of treatment with promin.

sporadic the affliction becomes apparent only from the histological examination of lesions. Biopsy reveals the bacilli in tissue sections and they may also be demonstrated from nasal discharges. It is said that the administration of a saturated solution of potassium iodide induces a nasal discharge from which the organism can be demonstrated.

More than 50 per cent of lepers without syphilitic infection have a *biologically false positive Wassermann reaction*. This is unfortunate and confusing since syphilitic gummas resemble the nodules of leprosy.

The anesthetic variety of leprosy may be confused with *syringomyelia* (p 1505). The presence of the cutaneous lesions and the enlarged palpable peripheral nerves in leprosy should lead to a correct differentiation.

A skin reaction has been described using a *lepromin antigen* in the manner in which tuberculin is employed. Early and late positive reactions are described *in 92 per cent* of lepers, the early response is an erythematous

* Parke Davis and Co Therapeutic Note June 1945 Courtesy of G H Faget Na
† Leprosarium Carville La

The tuberculin test is performed in a variety of ways. The *Von Pirquet* test is a scratch method, the *Mantoux* is an intracutaneous injection, the *patch test* is a percutaneous application. Either old tuberculin or P.P.D may be applied by any of these methods.

Mantoux Test.—For the Mantoux test two dilutions of O.T. or P.P.D. are made up and injected intracutaneously. If O.T. is used the initial test is 0.01 mg. or 0.1 cc. of a 1:10,000 dilution. If no reaction results the more concentrated dilution of 1 mg. or 0.1 cc. of 1:100 dilution should be given. If there is also no reaction with this dose the test is considered negative. If P.P.D. is used the initial dose is 0.00002 mg. and if that amount gives a negative test 0.005 mg. is used. See Fig. 34.

A *positive test* with either tuberculin is indicated by the development of edema and redness in the local area after forty-eight hours. Reactions which appear and disappear before that time are considered negative.

Patch or Percutaneous Test.—The patch test is a simple and practical modification of an older technic. Tuberculin is impregnated on gauze and applied to the skin on a strip of adhesive plaster. The test plasters are



Fig. 34.—Positive tuberculin reaction from intracutaneous test.

commercially available and are easily applied after cleansing the skin with acetone, ether, benzene or alcohol. A *positive reaction* consists of the development of red papules appearing after forty-eight hours. A control test rules out sensitivity to the adhesive itself. See Fig. 35.

The patch test is too new to evaluate accurately at the present time. Its ease of application makes it preferable for use in private practice. It is suggested that if the patch test is negative the Mantoux test should be done using the higher concentration of O.T. or P.P.D.

Reactions.—Tuberculin itself is not toxic and large amounts can be given to normal persons without effect. In the infected individual local, focal and general reactions occur. The *local tuberculin reaction* consists of the production of the Koch lesion. A small papule appears and persists after forty-eight hours with or without a slight lymphangitis or lymphadenitis. The *focal reaction* is a flare-up of a preexistent distant organ lesion, while the *constitutional disturbance* consists of a febrile elevation, tachycardia and malaise.

From Gay and Associates, *Agents of Disease and Host Resistance*. Courtesy of Charles C Thomas, Publishers.

CHAPTER 8

BACILLARY INFECTIONS HEMOPHILEAE

Pertussis (*H pertussis*)
Influenza (*H influenzae*)
Chancroid (*H ducreyi*)
Koch Weeks (*H conjunctivitidis*) (p 16[illegible]1)
Morax Axenfeld (*H duplex*) (p 16[illegible])

PERTUSSIS (WHOOPING COUGH)

WHOOPING COUGH one of the most prevalent of the acute communicable diseases is caused by the bacillus of Bordet and Gengou (*H pertussis*) The claim that the disease is produced by a filtrable virus with the bacillus in the role of a secondary invader has not been substantiated Pertussis can be reproduced in monkeys and in human volunteers by instillation of the organism and all of Koch s postulates have been fulfilled for *H pertussis*

Bacteriology —The bacillus described by Bordet and Gengou is a member of the *Hemophilus group of organisms* which also include *H influenzae* It is a tiny *gram-negative* non motile non spore forming cocco-bacillus On morphological grounds it is impossible to differentiate it from the influenza bacillus Like the latter it grows only upon a medium containing blood and requires the X and V factors (p 285) However it is less fastidious than *Hemophilus influenzae* and can be adapted in the laboratory to growth on simpler media

For primary isolation the medium described by Bordet and Gengou containing blood glycerine and potato extract is most suitable The organism is *hemolytic* on blood agar plates and when freshly isolated from human sources it is "*smooth* and *encapsulated* On prolonged laboratory cultivation rough forms develop the process of *dissociation* (p 143) from S to R taking place step-wise A number of phases of this transformation have been recognized and phase I corresponds to the smooth" freshly isolated organism while phase IV is the entire rough form

Fresh strains of *H pertussis* are antigenically homologous and belong to phase I These organisms possess maximum virulence and immunizing potency hence vaccines to be most effective must be made from smooth phase I cultures (Fig 17 p 138)

H pertussis produces a *toxin* which can be obtained from bacteria free culture filtrates and from the washed and ground up bacterial bodies themselves It is antigenic and capable of stimulating the production of *antitoxin* in experimental animals and in humans For purposes of immunization the toxin can be converted to a *toxoid*

Epidemiology —Whooping cough is *endemic* throughout the world It is most prevalent in the winter and spring but may occur at any season including summer In urban communities 80 per cent of the reported cases occur in children *under the age of five* and a considerable number of cases occur *under the age of one year* Unlike most other infectious diseases whooping cough occurs frequently in *the first six months of life* since there is apparently no passive transfer of antibodies from mother to fetus While in older children pertussis is a benign disease in infants under one year of age it is a severe disease with a case fatality rate as high as 25 per cent! The majority of deaths result from secondary pneumonia It is not generally realized that more children die annually from whooping cough than from measles and scarlet fever combined For some unknown reason the incidence and mortality of whooping cough are higher in females than males

The *communicability* of pertussis is high and in this respect, it resembles measles and chickenpox and differs from diphtheria and scarlet fever At least 75 per cent of the susceptible members of a family will develop the disease upon exposure P

tissue biopsy as in lesions of the skin and lymph nodes or by the examination of the tissues of the *injected guinea pig* (p 62)

PRESUMPTIVE DIAGNOSIS

The presumptive diagnosis of tuberculosis is unsatisfactory A positive tuberculin test the radiographic demonstration of suspicious lesions in the lungs the characteristic appearance of a dermatosis otherwise negative findings in a febrile or granulomatous process an idiopathic pleural effusion in an individual who has lived in contact with the acid fast marauder and a strong family history arouse the suspicions of the practitioner He is impelled to make frequent painstaking searches for the organism in sputum and the material that is swallowed and salvaged from gastric content or stool

CASE FINDINGS

One of the great triumphs of preventive medicine is the practical application of the principle of case finding in tuberculosis This technic requires tuberculin testing and radiography of the chest in the immediate contacts of the patient with active tuberculosis and of routine surveys among school children factory workers and those who apply for health examinations of one type or another The private practitioner is in the best position to practice preventive medicine when he places himself on his mettle at all times and applies the principles of case finding in his routine physical examination

ESTIMATION OF ACTIVITY

The definitive or presumptive diagnosis of tuberculosis is merely a first stage in the clinical problem Tubercle bacilli may be quite easily demonstrated in the sputum of a patient who has chronic fibroid phthisis with a well walled off cavitation and negligible activity In contrast organisms are not demonstrable in the most active disseminative phase of the disease such as the typhoidal variety of miliary tuberculosis Objective evidence is equally deceptive in the use of radiographs since a small fuzzy localized shadow in the infraclavicular region may transcend in activity a widespread fibro calcified complex with shadows of great extent

The index of activity is more accurately estimated by systemic than local findings The presence of fever tachycardia loss of weight loss of appetite asthenia easy fatigue and sustained rapidity of the sedimentation time point to the noxious influences of the invading organism These may be supplemented or corroborated by evidences of local spread as manifested by the presence of exudation or of fresh lesions in a radiograph of continued bleeding or fresh bleeding in genito urinary or intestinal disturbances or of new crops of lesions in the skin

RELATIONSHIP OF THE PRESENTING SYMPTOMATOLOGY

The final problem in the presence of tuberculosis is that of estimating the relationship of the infection to the presenting symptomatology Tuberculosis may be definitely diagnosed and active and yet bear no relationship to the complaints A not inconsiderable proportion of the population has suffered the primary infection and there is no reason why these people just as those few who are free from tuberculosis should not succumb to

gest the diagnosis of pertussis even in the absence of typical whooping During a paroxysm the child s face becomes suffused and livid and the attack may leave him limp and exhausted This is particularly true of young infants Older children seem to bear the attacks quite well with little impairment of nutrition or general condition

The paroxysmal stage lasts from one to six weeks or sometimes longer In mild cases it may subside in two weeks but in the average case it persists for about four weeks During this phase of the disease bilateral coarse rales and rhonchi characteristic of bronchitis can be elicited The presence of fine crepitant rales dullness or changes in breath sounds is indicative of a parenchymal pulmonary lesion The patient should be treated for pneumonitis although it should be borne in mind that *atelectasis* which may produce similar physical signs, is also a common complication of pertussis

Convalescence —After a variable period of time the paroxysms become less frequent and less severe and the vomiting ceases Then for about three weeks a tight hard cough remains Some children develop the habit of whooping which may persist long after the acute phase of the disease is over If an upper respiratory infection develops some weeks or months after an attack of pertussis it is not uncommon for the child to cough in paroxysms and even whoop Unless a cough plate (below) is examined this episode may be mistaken for a recurrence of pertussis In many instances the persistence of whooping may be the result of habit but some children use it as a device to attract parental attention

DIAGNOSIS

A suspicion of the presence of whooping cough in the catarrhal stage is often evident in the presence of an endemic or epidemic In the sporadic case the persistence of a dry hacking cough beyond a week or ten days without other adequate explanation should suffice to activate the practitioner to investigate the situation further by obtaining a white blood count and a *cough plate* The recognition of the disease during the catarrhal stage is of considerable importance from the standpoint of the prompt institution of methods of public health control and for the more effective symptomatic management

White Count —The white blood count is often of great value in establishing the diagnosis of whooping cough A relative and absolute increase in the number of small *lymphocytes* is characteristic of the disease In evaluating the leukocyte count it must be remembered that children under one year of age normally have 40 to 50 per cent of small lymphocytes and the average total leukocyte count may be as high as 12 to 13 000 per cu mm In pertussis the total white cell count per cu mm rises to from 14 to 35 000 with the percentage of small lymphocytes varying from 35 to 80 per cent These wide variations in the normal and diseased states make for difficulties in interpretation unless the changes are in the upper zones or show progression on repetition

Cough Plate —The definite diagnosis of whooping cough requires the identification of the *Hemophilus pertussis* by means of the cough plate A petri dish containing Bordet Gengou medium is uncovered held parallel to the patient s face and at a distance of 5 or 6 inches from the mouth dur

culosis Hence a specific curative effect from serum is not to be anticipated These considerations have not deterred the miracle men of medicine from exploiting the tuberculous by advocating the use of specific sera the most recent of which was the famous *turtle serum* This substance is mostly forgotten but it should not be long before other similar ventures are promulgated

Chemotherapy—Successful chemotherapy of tuberculosis has eluded earlier experimenters and clinicians but gold sulfonamide derivatives such as promin and streptomycin (p 104) have their present advocates

Streptomycin—A daily total of 3 0 gm of streptomycin injected intra muscularly in eight equal parts at three hour intervals appears to be of specific value in the treatment of incipient lesions progressively exudative infections ulcerative tracheo-bronchial tuberculosis and tuberculous men ingitis Treatment is continued for at least three months and requires supplementation with intrathecal administration in meningitis Alkaliniza tion prevents renal irritation but auditory neuritis is frequent after the third week of therapy Promin synergism may produce even happier results

Promin—The administration of Promin (p 98) diasone promizole or diamino diphenylsulfone and related drugs has proven to be useful in experimental tuberculosis of animals and there are those who believe they have noted progress in human infection Our own experiences hopefully instituted have proven to be thoroughly discouraging and we have aban doned the use of the drug but others report more enthusiastically of results obtained by the average oral dose of 1 gm (15 grains) given for four to twelve months

Gold—The use of gold in the treatment of tuberculosis is based on effects noted in lupus erythematosus (p 3396) Continental clinicians evinced considerable enthusiasm for chrysotherapy but American clin icians are more impressed by the toxicity of the drug (p 2922) than its therapeutic effectiveness Certainly injections of gold are too dangerous for use in private practice If they are to be employed the patient should be transferred to a sanitarium where treatment can be observed and con trolled by a phthisiologist experienced in the use of the drug

NONSPECIFIC TREATMENT

The nonspecific treatment of tuberculosis represents a great and humble triumph in modern medicine Its successful adoption is a tribute to the philosophical faith and courage of E L Trudeau who pioneered in its development The fundamental basis of the nonspecific treatment of tuberculosis is the practical application of the principle of rest so that the defensive mechanisms of the patient may be permitted to operate at optimum advantage In essence the aim is to sustain the development of the host reactions rather than to attack the invading organism

Rest—Rest is the touchstone for recovery in tuberculous infections It is an active and not a passive order (p 3754) It may involve putting the patient to bed splinting his involved extremity sedating his nervous sys tem or collapsing the infected lung

With active tuberculosis rest is measured in months and years rather than days and weeks Hence the initial problems involve home versus sanitarium care local versus climatic change

Bed Rest—Whether the patient remains home or goes to the sani

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use They become positive rather late in the course of the disease and are regularly found in all patients

Differential Diagnosis—In the absence of positive identification of *H pertussis in the cough plate* the diagnosis of whooping cough is made by inference A radiograph of the chest is taken to exclude parenchymal disease of the lungs particularly a *tuberculous infiltration* The upper respiratory passages are scrutinized for a *post nasal drip* due to inflammation of the accessory nasal sinuses, for enlargement of the *lingual tonsils* (p 2152) or for the presence of *foreign bodies* Should the child develop localized physical signs pointing to obstruction of a larger bronchus it is wise to consider the advisability of referring the patient to the specialist for *bronchoscopic observation*

The practitioner will recall that contacts may develop very atypical manifestations There may be merely a persistent cough without paroxysm cough plates are positive and infectivity particularly high since precautions are not taken with the diligence that would be followed were the more dramatic manifestations present

See *Differential Diagnosis of Commoner Febrile Skeletal Disorders* (p 192)

COMPLICATIONS

Of the major complications of pertussis *pneumonitis* is the most important since it accounts for the majority of deaths resulting from whooping cough It may be due to the pertussis organism itself or to secondary bacterial invaders as is discussed elsewhere (p 2185) Other respiratory complications include *atelectasis pneumothorax obstructive emphysema and bronchiectasis Atelectasis* results from the obstruction of a bronchus by a mucus plug The other pulmonary complications are very uncommon *Otitis media* is not frequent and is usually due to streptococci or other secondary invaders

Epistaxis is of fairly frequent occurrence in whooping cough *Conjunctival hemorrhages* and *purpura* may also occur Especially in infants paroxysms may terminate in a *convulsion* due to cerebral hemorrhage to gastric tetany secondary to the alkalosis of persisting vomiting to hypothetical toxins or cerebral anoxemia *Pertussis encephalopathy* is discussed elsewhere (p 447)

A minor but common complication is the development of an ulcer of the frenum under the tongue as a result of the protrusion of the organ over the lower central incisor teeth during a paroxysm *Umbilical hernias* and *prolapse of the rectum* may result from increased intra abdominal pressure during coughing attacks

TREATMENT

Since the treatment of the patient with whooping cough is mainly symptomatic and quite unsatisfactory the practitioner directs his best efforts toward preventive therapy in which he protects the general public by limiting the dissemination of the organism and conducts active immunization for the individuals who are under his personal care

Preventive Measures—The difficulty of diagnosing pertussis in the catarrhal phase when the infectivity is greatest results in a serious handicap in the attempt to satisfactorily isolate the reservoirs of infection Once the

Diet—The patient with tuberculosis should receive a full mixed relatively high calory diet He must be given as much nutrition as can be comfortably handled Stuffing will lead to opposition and gastric intolerance Nowhere in all of nursing is there a more difficult and demanding task than that of maintaining the nutrition of the tuberculous individual

For the most part appetizing well cooked simple foods are chosen Those articles which the patient enjoys are selected and he is not asked to take anything that fails to stimulate his palate The most important metabolic principle is the adequate supply of *protein* This should be no problem if meat fish poultry and eggs form the principal course of each of the principal meals and if the patient consumes the equivalent of a quart of milk daily Many patients do not object to drinking the beverage unchanged but others must be cajoled by the use of custards ice cream cheese and other dairy products

In the arrangement of the diet the physician should attempt to correct some of the current misinformation concerning metabolism Many people still believe that the ingestion of meat causes fever and that ice cream because of its palatability cannot be a nutritious food in comparison with chicken broth for example

There have been many attempts to introduce dietary fads in the regimen of the tuberculous patient Thus the impressive sounding *Gerson Sauerbruch Hermannsdorfer* diet is merely a salt free routine whose most salient characteristic seems to be its unpalatability The importance of calcification in the healing stages of the infection naturally suggested the use of *additional calcium* in the diet This is quite unnecessary if the equivalent of one quart of milk is ingested each day but the practitioner may add one or two grams of calcium lactate in powder form if anyone in the community has any faith in this principle

It was natural that the *vitamin fad* should strike the dietary regulation of tuberculosis and the enthusiasts for Vitamins A C D or B each advocate supplementary ingestion of the particular favorite Rather than attempt to swim against the stream for the present the practitioner does well to prescribe some multivitamin products

On occasions patients who fail to progress satisfactorily with dietotherapy increase their food intake when given 5 to 10 units of *insulin* fifteen or twenty minutes before each of the principal meals

The discussion on dietotherapy would not be complete without reference to *nicotine* and *alcohol* There is little doubt but that smoking decreases appetite and certainly the practitioner should forbid his patient to smoke before meals Many persons however derive considerable comfort from the habit of smoking and they should be permitted to puff on a cigarette at the end of a repast provided a sufficient amount of food has been stowed away

We are of the belief that *alcohol* is of positive benefit as an adjuvant to dietotherapy and psychotherapy A glass of sherry or port before meals and at bedtime stimulates appetite produces a glow of satisfaction and some relaxation and encourages sleep Those who are accustomed to stronger beverages may substitute a whiskey drink or some gin before the evening meal Cocktails are permissible but long drinks such as a whiskey and soda fill up too much valuable space and are to be avoided The patient

seems to be of definite value for the passive protection of susceptible children exposed to whooping cough It must be administered early in the incubation period and before the development of symptoms The protection afforded by antitoxin is short lived and its administration should be followed by a course of active immunization It would appear to be of greatest utility in young or debilitated infants definitely exposed to pertussis It is not a substitute for active immunization

Specific Curative Treatment —Specific curative therapy of pertussis is considerably less satisfactory than prophylaxis

Streptomycin, by intramuscular injection and aerosolization (p 2041) has produced seemingly excellent effects and merits trial Daily injections of 2 0 to 3 0 gm are suggested in six or eight doses The aerosol solution may be prepared in 100 000 units per cc (p 103)

At times *convalescent serum* and *hyperimmune globulin* (p 283) appear to be of some value in the amelioration of the severity of the attack if given in amounts of 10 to 20 cc by intramuscular injections The *sulfonamide drugs* may prevent or combat secondary infection with gram positive cocci

Symptomatic Treatment —The treatment of whooping cough beyond the catarrhal stage is largely symptomatic The child is kept in bed if fever is present Otherwise he is more comfortable out of bed and indeed *out of doors* The afflicted youngster is fed small frequent meals which are less apt to be vomited than large repasts When vomiting has occurred the child is fed immediately lest dehydration and acidosis result *Steam inhalations* are sometimes useful Whether they are medicated or not is a matter of indifference Occasionally a *warm bath* will relieve the child during a paroxysm An *abdominal binder or support* may prevent herniation

Drug Therapy —Drug therapy is most unsatisfactory An expectorant such as *Liquor Ammoniae Anisatus* may be given in doses of 30 drops diluted in one half glass of warm water at frequent intervals It is wise to sedate the child with *phenobarbital* in quarter grain doses three or four times daily The continued use of *cough drops* tends to produce nausea *Opiates* and *narcotics* induce constipation if given in amounts sufficiently large to control the cough reflex

A variety of other preparations has been recommended at one time or another Certainly *belladonna and its derivatives* which are widely used seem to be contraindicated since they tend to dry the membrane further and add to the tenacity of the offending mucus *Aminopyrine mixtures of chloral and bromide chlorbutanol antipyrine* and the like have their advocates but our enthusiasm for them is less than mild The rectal instillation of *ether in oil* using 4 cc for each year of age seems to be inadvisable

The sympatheticomimetic amines such as *ephedrine* and *neosynephrine* are also employed but the restlessness nervousness and tachycardia that develop after the prolonged administration of these preparations preclude their use

If there are evidences of fever and pulmonary involvement the *sulfonamides penicillin* and/or *streptomycin* are given for *prophylactic chemotherapy*

Roentgen Therapy —Though statistical evidence is unconvincing our own experience with roentgen therapy of the mediastinum if given in the

of any of the popular hypnotics at bedtime often accomplishes a more tranquil and more restful sleep

The popularity of *creosote* and *guaiacol* has fortunately waned since these drugs produce no benefit and often interfere with good appetite The advisability of giving *supplementary vitamin feedings* has been previously discussed (p 631)

We are opposed to the prescription of *belladonna* and its derivatives for the purpose of controlling night sweats If sufficient of the drug is given to control the sweat glands the dryness of the mouth interferes with swallowing and the dilatation of the pupils is a constant source of annoyance in reading We also oppose the use of *antipyretic drugs* since they produce an increase in sweat they may interfere with digestion and they cloud the temperature record which is of great value in estimating the course of the disease Should the patient be uncomfortable from hyperpyrexia *hydrotherapy* by the use of the sponge bath is greatly to be preferred

Psychotherapy—The successful conduct of the rest cure in tuberculosis requires supportive psychotherapy (p 1317) It is sometimes furnished by a heroic mother or wife husband or father but most often the physician is the symbol for strength and courage

Radio—The use of the radio has been a godsend to both patient and attendant in the conduct of the rest cure To be of its greatest value radio listening should be preferential A receiving set that drones all day long is a nuisance The choice of definite programs is made possible through programs that appear in the newspapers These make radio listening a boon of unlimited and immeasurable value for shut ins

Bibliotherapy—The first activity to be permitted the patient is the joy of reading As with the radio listening this should be given in directed dosage and supervised by some competent person In general newspapers magazines and light fiction are recommended Reading aloud is applicable particularly to children but is enjoyed by many adults The reading periods may be interspersed with listening to the radio so that the visual and auditory impressions are alternated

School children after a while may be permitted to resume their studies and receive their class assignments

Occupational Therapy—With stabilization of the infectious process the practitioner turns his thoughts to the institution of some form of occupational therapy This is usually simple for children who can draw cut out designs and play with especially devised toys for great lengths of time without boredom It is also simple with female patients who ordinarily are skilful at some type of work such as sewing knitting embroidery and the like It is not always easy for men but it is often amazing how many show a talent for various skills of one type or another (p 3760)

Visitors—Visitors may be a virtue or a curse in the sick room They are to be regulated by the physician in exactly the same way that he measures out medication Certain general principles are applicable to all cases Only one visitor is admitted at a time Visitors should come by appointment according to the patient s schedule rather than their own whims The visit should not exceed twenty minutes or perhaps a half hour Preference is to be given to visitors whose presence brings happiness to the patient This often means school companions business associates and

Clinical Manifestations

H influenzae produces several distinctly *localized inflammatory processes* which occur almost exclusively in infants and young children They *are accompanied by bacteremia and have an extremely high mortality* which has been sharply cut down by the recent extraordinary advances in specific therapy

INFLUENZAL MENINGITIS

The clinical features of influenzal meningitis do not differ in any significant manner from those of any other bacterial meningitis (p 213) An etiological diagnosis is made possible only by bacteriologic examination of spinal fluid or blood

In infants and children influenzal meningitis is second in frequency to tuberculous meningitis The portal of entry is the upper respiratory tract but *frank clinical infections of the ears sinuses or pharynx need* not necessarily precede the onset of the meningeal signs

The course of untreated influenzal meningitis may be acute and fulminating and culminate with death in a few days or it may be protracted for several weeks or even a month In the chronic cases thrombophlebitis of the lateral sinus or cerebral veins is a common finding

SUBACUTE BACTERIAL ENDOCARDITIS

Subacute bacterial endocarditis of influenzal origin does not differ in any way from the more common variety produced by alpha and gamma streptococci (p 1021) This influenzal infection is not limited to young infants and children but may be observed in younger adults

OBSTRUCTIVE INFECTION OF THE RESPIRATORY TRACT

Obstructive infections of the respiratory tract produced by *H influenzae* (type B) are uncommon but not rare The onset is abrupt and the course fulminating fatal cases terminating within twenty four hours of onset There is often a preceding mild upper respiratory infection after which *dyspnea* due to *laryngeal obstruction* sets in with amazing rapidity and becomes extreme within a few hours There is high fever The pharynx is red and edematous and the swollen epiglottis can be seen by depressing the tongue Direct laryngoscopic examination shows almost complete approximation of the swollen aryteno epiglottic folds against the posterior wall of the epiglottis Although the trachea larynx and bronchi are involved the dyspnea is due essentially to supraglottic obstructive edema

The picture of sudden *supraglottic obstruction* and *high fever* without membrane formation or loss of voice is clinically diagnostic of infection with *H influenzae* and specific treatment should be instituted accordingly Nasopharyngeal cultures usually are not significant since *H influenzae* (type B) are not readily recovered The organism can be identified and typed directly from mucopurulent material obtained from the larynx and the diagnosis may be confirmed by the result of blood culture, which is invariably positive

eased The affected nerve is palpated as an enlarged thickened cord like structure Eventually there is *loss of sensation* in the area of distribution with *atrophy* of the tissue supplied and at times loss of the parts due to



Fig 87—Nodular leprosy



Fig 88—Tubercular leprosy

spontaneous amputation Ulcerations may supervene especially on the digits

Aside from the atrophic and destructive changes in the skin there may also be present a *macular eruption* This rash is most commonly seen on

A few hours after the introduction of serum the patient s serum is obtained and diluted 1 10 with saline A Neufeld test is performed using the serum against the homologous influenza organism If capsule swelling occurs sufficient antibody has been introduced If the Neufeld test is negative the dose of serum should be repeated by intravenous injection

In the meningeal type of infection the course of the disease is followed by daily *lumbar puncture* If the spinal fluid becomes sterile and the sugar content rises steadily toward normal treatment may be discontinued gradually Under no circumstance is the sulfadiazine to be withheld until blood and spinal fluid cultures have been sterile for at least a week

Streptomycin —Streptomycin therapy (p 101) further supplements the specific results in *H influenzae* infections Parenteral and intrathecal injections of the antibiotic provide curative results alone and in combination with sulfonamide and serum

CHANCROID

Chancroid is a specific infectious disease transmitted through *sexual intercourse* It becomes manifest as single or multiple *ulcerations* of the genitals producing the appearance of the *soft chancre* to distinguish the affliction from the hard chancre of syphilis (p 336)

Bacteriology —The causative organism in the chancroidal infection is a small gram-negative *bacillus* first described by *Ducrey* and bearing his name In smears made from discharges of the ulcerated lesion and stained with methyl green pyronin (Pappenheim) the bacillus appears as a small ovoid rod arranged in pairs or groups The organism measures 1 to 1.5 μ in length and may be found within phagocytes or free in the exudate

The *Hemophilus ducreyi* is cultured on blood agar plates where it forms small grayish white colonies The etiological importance of the organism has been established by the reproduction of the disease in human volunteers injected with pure cultures In at least 90 per cent of the afflicted individuals the organism is readily identified in stained smears of exudates from the lesions

Clinical Manifestations

The *incubation period* of chancroid is short Within three to five days after exposure to infection a minute reddish *macule* appears at the site of inoculation which is usually genital and rarely extragenital The macule quickly becomes papular and in another twenty four to forty eight hours breaks down to form a small shallow *ulcer* Characteristically the ulcer has an inflamed areola but there is little induration as seen in the typical chancre of syphilis The ulcers are often *multiple* and coalesce by peripheral extension Secondary ulcerative lesions develop in adjacent areas by auto inoculation

In approximately half of the patients the *inguinal lymph nodes* become involved and may suppurate The adenitis may be unilateral or bilateral There is little or no *systemic reaction* to the genital ulceration unless suppuration occurs in the lymph nodes when there may be accompanying fever chills malaise and leukocytosis

The chancroidal infection is usually benign and heals spontaneously within a few weeks without specific treatment When secondary infection occurs particularly with streptococci there may be considerable local destruction of tissue and systemic disturbance of varying severity

infiltration that reaches maximum intensity forty eight hours after injection The late response is a papular or nodular reaction that occurs three or four weeks after the test injection

TREATMENT

Evaluation of specific therapeutic results in leprosy is difficult because of the protracted nature of the disease the rarity with which it causes death and the frequent spontaneous remissions

Promin—Encouraging results have been reported by the authorities of the Leprosarium at Carville Louisiana as the result of the treatment of leprosy with promin Oral doses of 1 gm (15 grains) for several months have appeared to give improvement verging on the specific The administration of promin however is not without danger (p 98) and may result in toxic manifestations such as exfoliative dermatitis leukopenia and anemia For the present promin therapy must be reserved for experimental use under hospital conditions

Chaulmoogra Oil—Chaulmoogra oil has been given as a specific in leprosy Most experts have little faith in its administration and certainly it is of no value in the treatment of tuberculosis where good reports have also emanated from uncritical enthusiasts

The oil is administered in a dosage of 0 3 cc three times daily Because of its nauseating taste and the gastro intestinal irritation weekly intramuscular injections of the ethyl esters of the fatty acid have been substituted The latter are exceedingly painful even when given in oil and in the Heiser mixture which contains equal parts of chaulmoogra and camphor oil with 3 6 per cent of resorcin The use of chaulmoogra oil is not without danger since renal irritation becomes manifest through albuminuria and hematuria Febrile reactions often develop with skin eruptions as further evidences of toxicity

Diphtheria Toxoid—In Thailand (Siam) where leprosy is rampant there have been reported remarkable results from the injection of *diphtheria toxoid* In the United States however these hopes for therapy have not been substantiated and the experiences thus far have been uniformly disappointing

Streptomycin—In view of the sensitivity of *M tuberculosis* (p 267) to streptomycin there is the possibility that the antibiotic (p 104) may prove of value in the treatment of infections with *M leprae*

Miscellaneous—Among other remedies that have been unsuccessfully tried in leprosy are arsenic gold smallpox vaccine methylene blue trypan blue brilliant green fluorescein dyes mercurochrome dilester (ethyl ester of dilo oil) calourogа oil cod liver oil vitamins strychnine hirudin Karwinskia latifolia and penicillin

DIFFERENTIAL DIAGNOSIS OF

Dermatoses of the Genitals and Perineum

There are few problems more difficult than this The wary practitioner mu t as ume that the disturbance is of venereal origin unle s he has definite proof to the contrary He cannot rest content until he has done a darkfield examination of open lesions for Treponema pallidum, a serologic te t for syphilis the Frei skin test for lymphopathia venereum and examined stained mears for H ducreyi (chancroid) and the Donovan bodies of granuloma inguinale

Despite these elaborate precautions experience reveals that non venereal dermatoses of the genital area are not uncommon Many patients suffer from lichen planus herpes simplex, scabies pediculosis pubis intertrigo dermatophytosis non pecific vulvovaginitis molluscum contagiosum condylomata lata most of which conditions pre ent clearly recognized morphologic features

CAUSE	DIAGNOSTIC FEATURES
Angioneurotic Edema	Urticarial lesion involving penis vulva or scrotum (p 3274)
Chancre	Vesicular papular and ulcerated with infiltration (hard chancre) and lymphadenopathy Darkfield positive but Wassermann negative
Chancroid	A venereal infection due to H ducreyi Lesion macular papular and ulcerative (soft chancre) Darkfield and serology negative Identify organism in stained smears (p 289)
Condylomata Acuminata	Flat non venereal moist papules in the uncleanly (p 2595) Darkfield and Wassermann negative
Contact Dermatitis	Nonspecific dermatosis from condoms venereal prophylactics etc (p 3274)
Cutaneous Horn	Precancerous warty projection Biopsy (p 3217)
Dermatophytosis	Fungous infection of thighs groins and moist areas Identify tinea (p 3309)
Epithelioma	Usually squamous cell with ulceration and adenopathy Biopsy (p 3223)
Erosive Balanitis	Fusospirochetosis (p 355) with dirty ulcerating slough Identify Vincent organisms and refer to expert for darkfield microscopy Wassermann negative
Erythroplasia	Rare precancerosis with dark red plaques Biopsy (p 3381)
Filariasis	Tropical disease with edema of scrotum or vulva and lymphadenopathy History of prevalence in locality (p 3321)
Granuloma Inguinale	Progressive ulcerating venereal disease Darkfield Frei test and serology negative Identify Donovan bodies by smear (p 475)
Herpes Simplex	Simple vesicle (p 433) Darkfield negative
Intertrigo	Particularly in skin folds in the obese and uncleanly (p 3161)
Leukoplakia	White elevated precancerous plaque usually due to chronic irritation Biopsy (p 3213)
Lichen Planus	Multiple flat violaceous papules Severe pruritus (p 3389)

NUED

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Treatment

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CHAPTER 9

BACILLARY INFECTIONS BACILLUS ANTHRACIS, CLOSTRIDIA, AND CORYNEBACTERIA

Anthrax (*B anthracis*)
Tetanus (*Cl tetani*)
Gas Gangrene (*Cl perfringens* etc)
Diphtheria (*C diphtheriae*)
Botulism (*Cl botulinum*)

ANTHRAX (MALIGNANT PUSTULE, WOOLSORTER S DISEASE)

ANTHRAX is a common disease of herbivora in many parts of the world Animals become infected by eating grasses contaminated with anthrax organisms or spores Man is accidentally affected by handling infected tissues skin wool hide or bristles In rare instances human infection follows the ingestion of improperly cooked or raw infected meat

In the United States human infections are fortunately rare due to the rigorous inspection of imported meat and wool However farmers veterinarians butchers slaughterhouse workers and those who handle and process hides wool and bristles are exposed to anthrax as an occupational hazard

Bacteriology and Immunology—The anthrax bacillus the first micro-organism conclusively shown to a have a specific relationship with the causation of human disease is a large gram positive encapsulated spore forming aerobic organism It grows readily on ordinary laboratory media and does not produce exotoxin By its capsule its type of growth in gelatin stab cultures and its pathogenicity for guinea pigs the anthrax bacillus is distinguished from other morphologically similar bacteria such as the hay bacillus (*B subtilis*)

Little is known of the mechanism of immunity to anthrax infection It is assumed to be a tissue response by phagocytosis since circulating antibodies are not detectable

CLINICAL MANIFESTATIONS

The clinical manifestations of anthrax are dependent upon the method of infection Cutaneous anthrax is characterized by the *malignant pustule* with the formation of local areas of necrosis and edema as described in the section on Diseases of the Skin (p 3272) The inhalation of the organism or its spores produces *woolsorter s disease* a fulminating type of pneumonia whose description is included in the section on Respiratory Diseases (p 2190) See *Differential Diagnosis of Commoner Febrile Skeletal Disorders* (p 192)

The cutaneous form of the disease has a mortality of 20 to 25 per cent in untreated cases while woolsorter s disease is almost always fatal The development of a septicemia is a grave prognostic sign in either type of disease

DIAGNOSIS

The diagnosis of anthrax is not difficult in the cutaneous form since the lesion usually has a characteristic appearance and the organism is easily

mitted by *droplet infection* The spread of the disease is facilitated by the difficulties in prompt recognition and isolation of patients Mild cases which never develop the typical whoop are quite common and are frequently missed Indeed without the help of the laboratory the diagnosis is sometimes impossible The missed cases are not isolated and serve most effectively to spread the disease in schools and institutions True healthy carriers are uncommon if they exist at all The disease is most infectious in the early catarrhal stage at which time the diagnosis is rarely made and in the first two weeks of the paroxysms After the fourth week of paroxysms the great majority of patients are no longer infectious

Immunity —Natural immunity to whooping cough is uncommon Most adults who claim to have escaped whooping cough actually have probably had mild and unrecognized attacks Young infants are not immune as there is no placental transfer of antibodies Acquired immunity as a result of an attack of whooping cough generally is considered to be durable and lasting but second attacks sometimes occur Following recovery from the disease agglutinins opsonins complement fixing antibodies and antitoxin can be demonstrated in the blood

Pathology —Whooping cough produces a *catarrhal inflammation* of the trachea and bronchi In the more severe cases the inflammation may spread down to the bronchioles as well There is secreted a great deal of mucus which is loose in the catarrhal stage but later becomes thick and viscid This material is irritating to the tracheal and bronchial surfaces and the effort to dislodge it initiates the *paroxysm of coughing*

Hemophilus pertussis organisms are present in *great numbers in the inflammatory exudate* in the trachea and bronchi but they are not commonly present in the uninvolved pharynx Hence in making a bacteriological diagnosis pharyngeal cultures taken in the usual way are useless The organism is only locally invasive and septicemia does not occur

Peribronchial infiltration of lymphocytes with edema congestion and interstitial pneumonitis are characteristic features of pertussis Enlargement of the tracheobronchial lymph nodes is a regular feature of the disease If secondary bacterial infection is superimposed an exudative intra alveolar reaction results leading to pneumonitis or even lobar consolidation The subject of pneumonitis in relation to pertussis is discussed elsewhere (p 918)

CLINICAL MANIFESTATIONS

The incubation period of pertussis varies from one to three weeks with an average of about fourteen days The clinical course of the disease is manifest as a catarrhal stage the stage of *paroxysms* and the stage of convalescence

Catarrhal Stage —The catarrhal stage is of variable duration but it usually lasts from one to two weeks During this phase a tight *dry hacking cough* is the chief manifestation Occasionally there may be low grade fever symptoms of rhinitis and sneezing Some malaise and listlessness are often present and the child may appear fretful and irritable During this period the cough increases in severity and frequency and is particularly troublesome at night After one or two weeks the cough becomes paroxysmal During the catarrhal stage the physical signs of bronchitis are not commonly elicited

Paroxysmal Stage —In the paroxysmal or whooping stage the clinical diagnosis is usually apparent The child will experience five or ten hard coughs during one expiration followed by a sudden deep inspiration which produces the characteristic crowing or whooping sound The next expiration is also accompanied by coughing followed by the inspiratory whoop There may be a number of such whoops in the course of one paroxysm In a case of average severity ten to fifteen such attacks may occur in the course of twenty four hours The paroxysms are worse at night and are usually less frequent if the patient is outdoors The paroxysm terminates with the expulsion of a plug of mucus and is commonly followed by *vomiting*

The presence of a paroxysmal cough followed by vomiting should sug

rience in the treatment of anthrax the high mortality of the disease would seem to justify a heroic method of combined treatment It would seem reasonable to set up an intravenous drip to deliver 200 cc of *anti anthrax serum* followed by 100 cc of 5 per cent *sodium sulfadiazine* Meantime intramuscular injections of *penicillin* might be administered in amounts of 100 000 units for the initial dose and 50 000 units at three hour intervals for subsequent doses It might be wise to reserve the more toxic arsenical until the effects of serum and the antibiotic agents had been ascertained It would be our suggestion if the arsenical were required to substitute *mapharsen* 60 mg for the considerably more toxic neoarsphenamine (p 119) *Purists may well criticize this form of shotgun therapy* but in a situation as desperate as anthrax the suggestion imposes a negligible risk in proportion to the potential gain

In overwhelming protracted or seemingly resistant infection especially in the weakened the aged and the very young high concentrations of penicillin effected by massive daily dosages of 500 000 to 1 000 000 units or by the production of blockade (p 109) are worthy of earnest consideration

Surgery—There is no possibility of employing surgery in respiratory manifestations Those with the greatest experience with malignant pustules regard local incision and excision as inadvisable procedures

TETANUS

Tetanus results from the liberation of powerful toxins by tetanus bacilli growing locally in human tissues It is a form of intoxication or poisoning affecting motor nerve cells and myoneural junctions The disease is characterized by an insidious onset an acute or chronic course lasting days or weeks generalized muscular spasm rigidity and tonic convulsions The mortality rate in untreated patients varies from *50 to* 70 per cent

Bacteriology—The tetanus organism belongs to the group of *Clostridia* which are widely disseminated in soil and are normal inhabitants of the intestinal tract of many herbivora *Tetanus bacilli may be present in human feces although not as often as* other members of this group of organisms such as *Clostridium welchii* Under ordinary conditions the organisms are harmless saprophytes

The Clostridia are rather large *gram positive bacilli* which grow anaerobically and form *spores* that are extremely resistant to heat drying and chemical disinfectants Tetanus spores have been shown to survive in soil for months or years and then under proper *conditions* the bacillary form is capable of elaborating a poison so powerful and lethal that as *little* as 0°5 mg is capable of killing a man

Tetanus toxin like diphtheria toxin is a true *exotoxin* and is *antigenic* It is because of this that *toxoid* and *antitoxin* can be produced for prophylactic and therapeutic use

Etiology—Tetanus usually results from the introduction of bacilli or spores into traumatic wounds Since the organisms are present in *soil and feces* contaminated wounds may be followed by tetanus

In civil life tetanus is rare although farmers stablemen and others who are likely to suffer soil-contaminated wounds have a greater likelihood of contracting the disease In time of war soldiers are in particular danger In World War I in which the action took place on cultivated soil the hazard was very great and led to the widespread prophylactic use of antitoxin

While the commonest cause of tetanus is the contamination of accidental wounds other portals of entry are also known Infection of the umbilical cord at birth leads to a highly fatal type of *tetanus neonatorum* which is rare in the United States but still common in the tropics *Surgical tetanus* from catgut sutures contaminated by tetanus spores is fortunately

ing a paroxysm of coughing If necessary a coughing attack is induced by touching the pharynx with a tongue depressor or swab When the patient coughs droplets of sputum containing the organism are sprayed onto the exposed plate After the specimen is obtained it is returned to the laboratory and incubated for forty eight hours after which time an experienced bacteriologist can readily distinguish the small white colonies surrounded by a zone of hemolysis (See Fig 40)

Cough plates are positive in over 50 per cent of whooping cough patients during the catarrhal stage Since clinical diagnosis is of greatest difficulty at this time the cough plate is a most valuable diagnostic aid



Fig 40—Use of the cough plate in the diagnosis of pertussis

although failure to obtain a positive result is not conclusive A higher percentage of *positive cultures can be obtained by the nasopharyngeal method* which involves passing a swab through the nose to reach the nasopharyngeal tissue

The percentage of positive results progressively decreases during the paroxysmal stage After the fourth week of the whooping stage the great majority of cough plates are negative

Other Laboratory Tests —Other laboratory methods in diagnosis include *agglutination complement fixation opsonocytophagic* and *skin tests* for hypersensitivity to *H pertussis* None of these is as yet adapted to general

Photograph by Dr Franklin H Top (Therapeutic Notes May–June 1943 Parke, Davis & Company)

Tetanus may be confused with acute meningitis poliomyelitis hysteria tetany strychnine poisoning or encephalitis If all the circumstances are considered especially a history of injury and the presence of a wound the diagnosis should not be difficult

PROGNOSIS

The overall mortality of untreated tetanus is 50 to 70 per cent The mortality rate is highest in young children and in patients over the age of 60 It is most favorable in the five to fifteen year age group An important feature of prognosis is the duration of the incubation period If it is longer than six days the patient has a 75 per cent chance to recover but if it is shorter than six days the prognosis is proportionately poorer In the most severe cases death may occur within three days of onset In general the longer the patient survives in the acute stages the better the ultimate prognosis Ninety per cent of deaths occur within ten days of onset Later deaths are commonly the result of pneumonia

The intensity and frequency of convulsions are also of prognostic importance The failure of adequate doses of sedative to control convulsions and relieve spasm is a grave sign

TREATMENT

Whereas the prophylactic treatment of tetanus is eminently successful the active management of the fully developed syndrome is far from satisfactory Tetanus after all is a relatively rare disease and opportunities for the clinical study of the various types of therapy are limited hence authorities disagree concerning many principles of treatment Despite these drawbacks the conscientious and vigorous application of accepted principles can be expected to reduce the overall mortality from the neighborhood of 60 or 70 per cent to 20 or 30 per cent

PREVENTIVE TREATMENT

The preventive treatment of tetanus is successfully carried out by *active immunization* before contamination has occurred and by the *passive method* upon receipt of the potentially infected wound

Active Immunization—The treatment of tetanus toxin with formalin results in a loss of toxicity without destruction of the specific antigenicity The resultant *toxoid* is employed for the production of artificial immunity and the more recently popularized *alum-precipitated toxoid* is now most widely used often in the preparation combined with diphtheria toxoid

Alum Precipitated Toxoid—Two injections of 1 cc each of alum precipitated toxoid given at intervals of one or two months result in a *fairly high level of antitoxic immunity* which persists for six months to a year At the end of this time a booster dose of 1 cc restores the titer of antitoxin within five days after the injection The level of antitoxin produced in this brief period equals that ordinarily acquired by the administration of the usual 1500 unit dose of antitoxin

It is possible by this method to produce active immunization with *yearly stimulating doses* of the alum precipitated toxoid Should the patient receive an injury any time within a year of the last injection it is sufficient to give another dose of toxoid which precludes the necessity of administering the antitoxin (see p 297)

diagnosis has become obvious in the paroxysmal stage the patient is instructed to avoid spraying the organisms but even these precautions are usually ineffectual since infants cannot cooperate and older children during a paroxysm are in no condition to exert voluntary control over their actions These circumstances encourage the practitioner to induce active immunization of all susceptible children in the hope of accomplishing a reduction in the incidence of the disease by protecting each individual

Active Immunization —Active immunization may be carried out in whooping cough by means of a *pertussis vaccine* made from a freshly isolated smooth phase I organism For practical purposes it is best to use the intermediate strength preparation containing 15 000 000 organisms per cubic centimeter In this the bacteria are killed by the addition of 0.5 per cent phenol and refrigeration for one week The full immunizing dose is 7 cc given in three injections At the first injection 1 cc is injected into the left deltoid region at the second injection 2 cc are injected into the right deltoid region at the final injection 2 cc are put into the left triceps region and 2 cc into the right triceps region Local reactions are moderate and protection is very complete

As an alternative a *detoxified pertussis antigen* has been prepared from a formalized filtrate This is particularly useful as a prophylactic before and after exposure to whooping cough and may also be used for treatment in early phases of the disease For general prophylactic use three subcutaneous injections of 2 cc are administered at intervals of a week for immunization of direct contacts and for curative use 1 5 to 2 cc are given subcutaneously in three to five doses at intervals of forty eight to seventy two hours

For general prophylaxis pertussis vaccine in the strength of 20 000 000 per cc may be combined with both *alum precipitated diphtheria and tetanus toxoids* Children between the ages of six months and one year should be routinely protected by the injection of two 1 cc doses of this combination with 1 cc of the pertussis vaccine (20 000 000 to the cc) interspersed so that 50 000 000 are introduced for the total amount Abscesses may be prevented by deep subcutaneous or intramuscular injection using a fresh needle and rejecting the needle with which the vaccine was withdrawn from the vial

These vaccines do not confer absolute immunity but they completely protect 28 per cent against 5 per cent of controls and are followed by severe infection in 22 per cent against 35 per cent in controls Complications of pertussis are reduced from 18 per cent in the controls to 0 06 per cent in the protected

Passive Immunization —If a young infant is exposed to whooping cough it is desirable to attempt to prevent or modify the disease *Convalescent serum* in doses of 10 cc intramuscularly appears to have definite value in prophylaxis Because of the difficulty of obtaining convalescent serum some workers have resorted to the vaccination of adults in order to secure *hyperimmune serum* Encouraging results have been reported from the injection of 25 cc of a highly concentrated and purified globulin repeated in twenty four hours preferably during the period of incubation

Concentrated antitoxin can now be produced in rabbits immunized with toxin or toxoid Antitoxin has no obvious therapeutic efficacy but

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catarrhal phase has been most encouraging in individual instances If facilities are available certainly this method should be tried Others advocate exposure to *ultraviolet light* and this can do no harm

INFLUENZA BACILLUS

The influenza bacillus (Pfeiffer s bacillus or *Hemophilus influenzae*) is a common inhabitant of the upper respiratory tract Ever since Pfeiffer isolated the organism in the pharynx of patients with influenza there has been confusion in regard to the relation of this organism to the disease It is now clear that influenza is a virus disease (p 387) and is not produced by Pfeiffer s bacillus which unfortunately still bears the misnomer influenza bacillus The bacillus however may produce respiratory disease as well as subacute bacterial endocarditis and a highly fatal type of meningitis (p 286)

Bacteriology —*H influenzae is a very small rod* at times almost coccal in form It has a tendency toward *pleomorphism* and while the majority of cells in a culture may be coccobacillary others may be long and threadlike forming tangled masses This pleomorphism is one of the characteristic morphological features of the organism which is nonspore forming non motile and gram negative

Hemophilus influenzae requires an enriched medium for growth The failure of the organisms to grow in the absence of blood or certain factors *present in blood* is so characteristic that the *name* Hemophilus is derived from this fact It has long been recognized that *two* specific growth factors are essential *the X factor* is a derivative of hemoglobin and the *V factor* is present in many plant and animal tissues The X factor is thermostable and contains iron The V factor is thermolabile and its active component is co-enzyme I (cozymase) The observation that *H influenzae* grows profusely in the immediate neighborhood of staphylococcus colonies is probably explained by the fact that the latter *supply* co-enzyme necessary for the growth of the former

H influenzae apparently represents an organism with such a high degree of parasitism that it has lost the *synthesizing* ability which most bacteria possess It is most conveniently grown *on* chocolate agar but other suitable media containing the X and V factors have been devised

Both *smooth* and *rough* strains of the influenza bacillus occur They differ in colony appearance antigenic structure and their disease producing potentialities *Smooth strains* are encapsulated and on the basis of differences in capsular polysaccharides have been divided into types A to F Virtually all the serious infections *are* due to *smooth* strains of type B (Pittman s classification)

Smooth strains can be typed by *precipitin* tests using the Neufeld technic in a manner identical with the typing of pneumococci (p 901) When smooth encapsulated *H influenzae* are mixed with *homologous* type specific antiserums capsular swelling can be demonstrated and *the* type *quickly* determined Special care must be taken to use cultures of influenza *bacilli less than* six hours old In older cultures the capsules degenerate unless the *organisms* are preserved with formalin Rapid typing can be done directly on spinal fluid containing influenza bacilli on blood cultures or empyema fluid or on mucopurulent material obtained at tracheotomy in patients with obstructive laryngitis The diagnostic antiserums used for Neufeld typing are commercially available for type A and B the latter being the *most* common pathogenic type *Rough* strains are not encapsulated and are most commonly recovered from normal or diseased respiratory membranes where they appear to be harmless or at best secondary invaders

Immunity —Infection with *H influenzae* is limited almost entirely to infants and children The explanation for the selectivity of *infection* lies in the immune status of normal *persons* The *blood of newborn infants* has bactericidal activity against the *H influenzae* This property is *passively transferred* via the placenta and is soon lost so that *infants* from six to eight*een months* of age have no protective antibodies The successful accomplishment of natural immunization is evidenced by the fact that older children possess a universal ability to destroy the organisms when they gain access to the blood *stream*

these circumstances to subject the patient to the disturbance and trauma of lumbar or cisternal puncture (p 3783) For optimal antitoxic activity *intravenous administration* is preferable and the serum should be administered by the drip method The usual skin and conjunctival sensitivity tests are done and the patient is questioned concerning preceding injections of horse serum or manifestations of allergy If there is any question of sensitivity the intramuscular route of administration is safer or the Tetanus Antitoxin Bovine N N R may be substituted Desensitization (p 86) is required in those who react abnormally to horse serum injections It may be anticipated that serum sickness will develop in five to ten days in approximately 25 per cent of the patients who are treated with antitoxin

THE ANTI INFECTIVE AGENTS

The *sulfonamides* appear to have no specific value in the treatment of tetanus They may have secondary value due to their effects on susceptible or sensitive secondary invaders *Penicillin* has clearcut activity on all clostridia including the tetanus organism It should be given in conjunction with serum therapy in large doses administered intravenously In overwhelming protracted or seemingly resistant infection especially in the weakened the aged and the very young high concentrations of penicillin effected by massive daily dosages of 500 000 to 1 000 000 units or by the production of blockade (p 109) are worthy of earnest consideration

COMBINED SPECIFIC TREATMENT

It is recommended that the use of the immunological agent and the anti infective preparation be combined in a continuous intravenous drip So serious is the infection of tetanus that it is far better to err on the side of overtreatment An intravenous drip may be established through which alternating injections are delivered of diluted tetanus antitoxin and penicillin Of the former at least 100 000 units should be the daily dose and of the latter as much as 500 000 units may be delivered with safety

SURGERY

Wide incisions excisions and even amputations are practiced by surgeons as emergency measures to remove the focus which is feeding toxin into the body We do not favor this radical attitude since the symptoms of tetanus are the result of toxin already fixed in the nervous system and the toxin which is subsequently liberated from the wound can be neutralized effectively by the administration of antitoxin We hold that the treatment of the local wound should be no more or less than would be required if the patient did not have tetanus Efforts should be made to remove foreign bodies and debris The tissues surrounding the wound are infiltrated with antitoxin before surgical procedures are attempted

SUPPORTIVE AND NURSING CARE

The constant attendance of trained nurses is absolutely essential to the successful treatment of tetanus The room should be kept darkened and quiet Fluid balance is maintained by mouth feeding if possible or parenterally if necessary Intravenous injections are better tolerated and

PNEUMONIA

In children *H influenzae* may cause a primary pneumonia (p 2171) clinically indistinguishable from pneumococcal infection In infants less than a year old *H influenzae* pneumonia is extremely serious with a high case fatality rate *Bacteremia* is a common feature of the disease and *empyema* a frequent complication There is also a high incidence of secondary *influenzal meningitis* and in such patients the prognosis is nearly hopeless

See *Differential Diagnosis of Commoner Febrile Skeletal Disorders* (p 192)

BACTEREMIA

Hemophilus influenzal bacteremia accompanies the meningeal obstructive and pneumonic manifestations of invasion with this organism In the absence of any of these localizing disturbances it may be assumed that the bacteremia is the result of a subacute bacterial endocarditis

TREATMENT

Prior to the introduction of specific serum sulfonamides and antibiotics the mortality of *H influenzae* bacteremia and meningitis approached 100 per cent With recent innovations in excess of 75 per cent have been cured These remarkable advances in therapy require special forms of laboratory checks possible only in the well equipped institutions Hence the practitioner owes it to himself and his patient to supervise the removal of the afflicted individual to the nearest hospital where the special facilities are available

Sulfonamide Therapy—As soon as the clinical diagnosis of influenzal infection has been established by spinal fluid or blood culture an initial intravenous dose of 0 075 gm per kilogram of sodium sulfadiazine is injected This involves the introduction of 10 cc of 5 per cent solution in the patient who weighs 25 pounds The dose is repeated in six hours and thereafter 0 02 gm are given per kilogram at four hour intervals If possible the subsequent doses are administered by mouth When sulfonamide therapy is combined with serum therapy it is technically simpler to establish an intravenous drip under which circumstance the sodium sulfadiazine is given in 2 per cent concentration in saline

Serum Therapy—Whereas the sulfonamide drugs alone have been responsible for a number of cures the percentage of successful results is sharply increased by employing combination therapy using a *homologous type specific concentrated anti influenza rabbit serum* Since this material is not available for general distribution the practitioner must rely on chemotherapy alone until he can locate a supply of the specific substance The *horse serums* that have been previously employed in the treatment of influenzal bacillus meningitis especially seem to be much less effective than the homologous rabbit preparations

Where facilities are available the offending organism is typed by a direct Neufeld examination of the spinal fluid The bacillus is also tested against the serum to be used and if it is antigenically suitable an intravenous injection is made using an amount of serum containing 50 mg of antibody nitrogen for the case of average severity

toxin and the rapid control of the motor disturbances by the guarded introduction of sodium pentothal or paraldehyde

GAS GANGRENE

A number of *Clostridia* infect wounds and produce a spreading edematous necrosis or gangrene of tissue, accompanied by the formation of *gas*. These effects like those of the tetanus bacillus are caused by *exotoxins* and the organisms commonly involved in the production of gas gangrene are *Cl welchii Cl septique Cl oedematiens Cl sporogenes Cl histolyticum* and *Cl fallax*. Of these the first three are the most important. They are ubiquitous in soil and streets and *Cl welchii* is a normal inhabitant of the human intestinal tract.

Bacteriology—The Clostridia are *gram positive anaerobic bacilli* which form resistant *spores*. The pathological effects which they produce are largely the result of the action of their *toxins*. These toxins are *antigenic* and they are destroyed by heat (70 C) or weak acids. They are *hemolytic* especially that of *Cl welchii* which may account for the rapid anemia associated with this infection. They also possess *leukocidic* properties and *Cl welchii* and *Cl septique* are *saccharolytic* producing large amounts of gas in the tissues. *Cl histolyticum* is *proteolytic* and liquefies tissue.

CLINICAL MANIFESTATIONS

Gas gangrene is chiefly a *complication of dirty infected wounds*. However since *Cl welchii* is normally present in the human bowel the organism is sometimes responsible for *peritonitis* an occasional *pelvic infection* or *sepsis following instrumentation* especially self induced abortion and penetrating wounds of the perineum by impalement.

The clinical picture of gas gangrene may vary from mild edema of the traumatic or surgical wound to massive swelling palpable subcutaneous crepitation and eventual sloughing gangrene. Thin dirty fluid with gas bubbles escapes from the grayish brown wound edges. There may be profound general toxemia high fever and leukocytosis with death in a short time. Fulminating cases apparently develop *acute adrenocortical insufficiency* and show pathological lesions in that organ at autopsy. *Bacteremia* is often present in severe cases.

Little is known about natural immunity to gas gangrene since recovery from an attack does not appear to confer any lasting protection.

DIAGNOSIS

The definite diagnosis of gas gangrene is made by *bacteriological culture of the blood or the local lesion*. The clinical diagnosis is suggested by the presence of *edema* and *crepitation with a blood tinged malodorous discharge*. It is not always possible to estimate the amount of tissue involvement by the appearance of the skin since little actual gangrene may be evidenced in the epidermis. Gas gangrene is usually a mixed infection with *Cl welchii Cl septique* and *Cl oedematiens*.

TREATMENT

PREVENTIVE TREATMENT

Although toxoids for the clostridia of gas gangrene are produced methods of *active immunization* are not yet available. *Passive immunization* is highly recommended when the need arises the available prepara

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Roentgen Therapy—Radiation therapy is of uncertain value in the treatment of gas gangrene It has been enthusiastically acclaimed by some clinicians but it is considered worthless by others In any event it can do no harm and may be applied locally to the wound without any risk of untoward effects

DIPHTHERIA

Diphtheria is an acute infectious disease due to *Corynebacterium diphtheriae* It is characterized by invasion of the nasopharynx and larynx the local production of membranes and by constitutional symptoms due to the effects on distant organs of a powerful specific exotoxin

Bacteriology—The diphtheria bacillus (often called the *Klebs Loeffler bacillus* in honor of its discoverers) is the principal member of the group of *Corynebacteria*, so named because of their club-like shape Many of the members of the group are normally present on

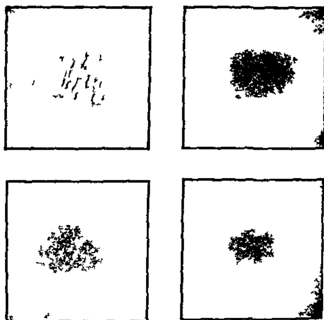


Fig 43—Positive Schick tests

the skin and mucous membranes of man where they are saprophytic or of doubtful pathogenicity Among the common diphtheroids are *C hoffmannii* which is frequently present in the throat and *C xerose* which is sometimes found in conjunctivitis although its pathogenicity is questionable Numerous other less clearly defined diphtheroid organisms also exist On morphological grounds expert bacteriologists can usually differentiate *C diphtheriae* from diphtheroids but it may be necessary to carry out cultural biochemical and virulence tests in order to make the distinction with certainty

Diphtheria bacilli are straight slender rods varying from 1.2 to 6 4 microns in length They are rarely of uniform thickness throughout their length and generally have club-shaped thicknesses at one or both ends In stained smears they show a characteristic grouping lying in small clusters parallel to each other or at sharp angles Frequently adjacent bacilli are arranged in the form of a V or Y and branched forms have also been described *C diphtheriae* is *gram positive* but its morphological characteristics are best brought out by staining with Loeffler s alkaline methylene blue solution With this stain the organisms have a banded or beaded appearance so that on superficial examination they may resemble short

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DIAGNOSIS

The clinical suspicion of chancroid must be confirmed by definitive demonstration of the Ducrey bacillus in the stained smears of pus obtained from the ulcers Simultaneously the practitioner eliminates the possibility of a superimposed or associated *syphilitic infection*

In addition to the direct microscopic examination an *intradermal test* has been devised using as test material the Ducrey antigen which is commercially available A dose of 0 1 cc is injected intradermally in the forearm The *positive reaction* develops in forty eight hours as a papule 10 mm in diameter surrounded by an areola The patient with chancroidal infection develops skin hypersensitivity within eight to fourteen days after infection If the test is negative two weeks after infection it is unlikely that chancroid is present The test remains positive for an indefinite time



A B

Fig 41 —A Chancroidal lesion of penis B Chancroid skin test (48-hr reading)

and does not prove that a given lesion is chancroidal but merely indicates that the patient is infected or has been infected in the past (See Fig 41)

See *Differential Diagnosis of Dermatoses of Genitals and Perineum* (p 290)

TREATMENT

The chancroid infection is generally a benign lesion which heals spontaneously if treated with ordinary *hygienic care* Prior to the successful introduction of *chemotherapy surgical measures* included circumcision or incision and drainage of suppurative adenitis

Chemotherapy—The introduction of the *sulfonamide compounds* has completely altered the treatment of the chancroidal infection Any of the soluble derivatives may be used and perhaps *sulfadiazine* is the preparation of choice With small dosage such as 6 gm (90 grains) for the first three days and 3 gm (45 grains) daily for a week or ten days thereafter healing will occur within a short time and a recent report recorded no failures of

cutaneously with a culture of diphtheria bacilli or with the filtrate from a toxin producing strain the animal will die in a few days Diphtheria toxin was originally standardized by this technic and the M.L.D (minimum lethal dose) was defined as the smallest amount of toxin which when injected subcutaneously into a 250 gm guinea pig killed the animal in four days In practice in order to perform a number of virulence tests at the same time and to avoid the death of the animals the injection is made intracutaneously and is controlled by administering antitoxin Two animals either rabbits or guinea pigs are required The growth of organisms on a Loeffler s slant is suspended in broth and 0 1 cc is injected intracutaneously into the shaved skins At the same time one of the animals is given 500 or 1000 units of diphtheria antitoxin intraperitoneally If the culture is virulent and produces toxin the unprotected animal develops an indurated area with necrosis of the skin at the site of the injection in forty eight to seventy two hours whereas the animal protected by antitoxin develops no lesion

The Schick Test—The Schick test involves the intradermal injection of 1/50 M.L.D of *diphtheria toxin* the reaction to which indicates the presence or absence of antitoxin in the subject s blood The test has been of inestimable value in determining *susceptibility to diphtheria* and consequently indicating those individuals who are in need of *active immunization* (p 76) It was formerly thought that a negative skin reaction indicated the presence of at least 1/30 unit of antitoxin in the blood More recent work has shown that as little as 1/60 unit of antitoxin is sufficient to neutralize this amount of toxin and give a negative test

Technic—The Schick test is performed by injecting 0 1 cc of toxin intradermally on the inner surface of the forearm making sure that a wheal is produced The official toxin is already diluted for use and 0 1 cc contains 1/50 M.L.D It is buffered so that it remains stable for long periods of time Since false positive reactions may occur a control injection is necessary using diluted Schick toxin boiled for one hour or diluted toxoid (Maloney test) (p 310) The control is applied on the other arm in an exactly similar manner

Reactions—A *positive reaction* reaches its height in five to seven days at which time false positive reactions have generally disappeared A positive reaction is indicated by a zone of erythema and induration varying in size from a quarter to a silver dollar Any reaction larger than the control and more than 0 3 cm in diameter persisting for five to seven days should be considered positive and therefore indicative of lack of antitoxic immunity

A *negative control reaction* shows at most a small papule or erythema at the site of injection no larger than 0 3 cm in diameter

False positive reactions appear from six to eighteen hours after injection reach their height in thirty six to forty-eight hours and generally disappear by the fourth or fifth day The false positive reaction is present on both the control and test sites and indicate that the reaction is due to some substance present in the injected material other than toxin itself

Confusion in the interpretation of the Schick test may be avoided by waiting until five to seven days after the injection before reading the test Positive reactions fade slowly leaving an area of brownish pigmentation which may persist for several weeks

UNTOWARD REACTIONS—Untoward reactions resulting from the Schick test are quite uncommon A few instances of localized and generalized urticaria *angioneurotic edema* and *asthmatic wheezing* have occurred in persons previously immunized and probably sensitized to the buffering agents used in the toxin In view of the great number of Schick tests performed constitutional reactions are exceptional and fear of them should not deter the practitioner from performing the test

Interpretation—There is overwhelming evidence that *the Schick test is a reliable indicator of susceptibility or immunity to diphtheria* The test should be performed on contacts carriers of diphtheria bacilli and adults who are to be immunized for the first time In the case of infants who are to receive active immunization it is not necessary to perform a preliminary Schick test since after the age of six months the great majority are Schick positive (susceptible) A Schick test should always be performed several months after a course of immunization to determine whether immunity has been successfully established *Children who were immunized before three years of age should have the* Schick test repeated on entrance to school so that positive reactors can be reimmunized

Epidemiology—Diphtheria is of world wide distribution It is common in temperate and colder climates and rare in the tropics The peak of its annual incidence occurs in the early winter months of the year The majority of patients are in the group from one to ten

Lymphopathia Venereum	Primary vesicle darkfield negative Later bilateral lymphadenopathy with positive Frei test (p 471)
Melanocarcinoma	Black malignant nodule Biopsy (p 3225)
Molluscum Contagiosum	Umbilicated vesicles of virus origin (p 3287) Darkfield negative
Moniliasis	Yeast infection in diabetics and pregnant Identify monilia (p 3301)
Pediculosis Pubis	Intense pruritus with identification of crabs or nits (p 3185)
Scabies	Intense nocturnal pruritus with characteristic burrows and excoriations Identify parasite (p 3180)
Senile Vulvovaginitis and Kraurosis Vulvae	Atrophy fissuring pruritus and leukoplakia in elderly females Administer estrogen (p 2597)
Syphilis	Secondary syphilids may be flat soft condylomas (p 338) Darkfield and Wassermann positive See also Chancre
Tuberculous Chancre	Chronic ulcer following ritual circumcision Get smears and biop y (p 51)

treatment Following healing of the chancroid the patient should report weekly for two months for observation and serologic tests for syphilis Circumcision is postponed for three months Penicillin is withheld since it is therapeutically useless and may mask concurrent syphilis

Prophylactic chemotherapy has also proven successful in chancroidal disease The administration of 2 gm (30 grains) of sulfadiazine to a group of soldiers before leaving camp another 2 gm (30 grains) on their return and a final dose of 2 gm (30 grains) the next morning reduced the incidence of chancroidal infection from 52 to 6 per thousand

Clinical Manifestations

The *incubation period* of diphtheria is two to five days The clinical types of diphtheria differ in the location and extensiveness of the membrane in toxicity and in the frequency of complications Diphtheria may be classified as tonsillar nasopharyngeal laryngeal nasal and septic

TONSILLAR TYPE

At the present time more than half of all diphtheritic infections are of the tonsillar type The onset is insidious rather than abrupt The temperature is only moderately elevated and rarely exceeds 103° F Sore throat and difficulty in swallowing are not marked which is rather unfortunate *since it does not quickly direct attention to the lesion* The tonsillar and pharyngeal mucosa are dusky red not brightly injected and edematous as in streptococcal pharyngitis or scarlet fever The *membrane* first develops on one tonsil and then spreads to the other The tonsils swell until they almost meet in the midline The membrane is thick and grayish white or greenish gray in color and it can be removed *only with difficulty* leaving a raw bleeding surface By contrast streptococcal exudates are less extensive more follicular thinner and more easily brushed off

In typical diphtheria of moderate severity there are *tachycardia* and a variable degree of *prostration* *Leukocytosis* of from 10 to 20 000 per cu mm is commonly present There is a characteristic fetid *odor to the breath* (Fig 44 p 303)

If the patient is untreated the fever and the membrane persist for four to seven days With adequate treatment the case fatality of this form of diphtheria is quite low and complications are uncommon

NASOPHARYNGEAL TYPE

The nasopharyngeal type of diphtheria is usually severe The *membrane* spreads rapidly involving tonsils uvula and posterior nasopharyngeal wall When the membrane begins in the posterior nasal mucosa and spreads down behind the soft palate involving the posterior surface of the uvula it is demonstrated best by pushing the uvula up and forward with a tongue blade In this type of diphtheria *toxemia* is profound because of the large surface of membrane from which toxin can be absorbed

The symptoms begin insidiously but progress steadily reaching their maximum intensity in four or five days There is obstruction to nasal breathing and difficulty in swallowing The cervical glands and the tissues of the neck may be markedly swollen resulting in the so called bull neck ' Cardiac complications are common and death may occur within the first week from toxic myocarditis although the usual symptoms of cardiac involvement do not appear before the seventh day Febrile albuminuria is regularly present

The local process in the nasopharynx reaches its height by the fifth or sixth day and two or three days later the membrane begins to loosen As the membrane disappears the local symptoms such as discharge from the nose and throat cervical swelling noisy breathing and difficulty in swal

isolated The pulmonary type has no clinical features of specific diagnostic value although an occupational history should arouse suspicion in the presence of an atypical severe respiratory infection The microscopic identification of the organisms in stained smears of sputum or pus should be confirmed by cultures and animal inoculation tests since *B subtilis* and other saprophytes morphologically similar to anthrax are common contaminants

Treatment

The specific therapy of anthrax includes the use of an *antibacterial serum* and of *chemotherapeutic agencies* Additionally in cutaneous anthrax the question of *surgical interference* requires consultation with an experienced specialist

Anti anthrax Serum N N R—Anti anthrax serum is effective if administered early in the disease in large amounts Its prompt use has reduced the



Fig 42—Malignant pustule of anthrax *

mortality of the cutaneous forms to less than 10 per cent but the prognosis of pulmonary forms still remains extremely high

The serum is administered intravenously in an initial dose of 200 cc Unless there is striking clinical improvement the injections are repeated at twelve to twenty four hour intervals The criterion of successful therapy is the prompt subsidence and the control of the edema that surrounds the cutaneous pustule In the woolsorter s disease there is unfortunately no such visible guide

Chemotherapy and Anti infective Agents—Prior to the introduction of the anti infective agents reports of the successful use of *neoarsphenamine* emanated from South Africa where the disease is prevalent Neoarsphenamine 0 6 gm is recommended to be given intravenously with repetition in twenty four hours if necessary

Preliminary laboratory and clinical investigations suggest some beneficial effects from sulfonamide and penicillin While we have had no expe

* Courtesy of New York City Department of Health

pneumonia myocarditis and *nerve palsies* are uncommon Pneumonia is most often seen as a complication of laryngeal diphtheria while myocarditis and neuritis which are the direct results of poisoning by diphtheria toxin are more common in the severe nasopharyngeal forms since this type is characterized by extensive membrane formation with greater absorption of toxin

MYOCARDITIS

In fulminating cases death from toxic myocarditis may occur suddenly and with little warning during the first week of the disease Much more commonly however symptoms of myocardial and circulatory involvement develop during the second week of the disease and they may not appear until the third or fourth weeks

With myocardial involvement the pulse becomes rapid and weak and the blood pressure falls The muscular quality of the first heart sound is lost *Arrhythmias* particularly partial or complete *heart block* (p 879) are encountered When involvement of the myocardium is less extensive the only abnormality may be a prolongation of the P–R interval or inversion of the T waves in Leads I and II

The *prognosis* in the presence of myocarditis should be guarded If the patient survives for a week or ten days recovery is anticipated but prolonged and complete bed rest is indicated

NEURITIS

Paralysis as a result of toxic neuritis is one of the most important sequels of diphtheria occurring in from 5 to 20 per cent of all hospitalized patients The muscles of the *soft palate* are generally first affected and may *be the only ones involved It will be noted that the voice has* become nasal in quality and the uvula can be seen to hang limp The *pharyngeal muscles* also may be involved leading to difficulty in swallowing and regurgitation of food and fluids through the nose The *extra ocular muscles* are not uncommonly affected causing *strabismus* and *diplopia*

At times the muscles of the *neck trunk* and *extremities* become paralyzed and in rare cases the *phrenic nerve* is involved resulting in respiratory distress If both the diaphragm and intercostal muscles are affected death may result from asphyxia

The *prognosis* of the neuritides as far as return of function is concerned is excellent, so that if the patient can be tided over the critical week or ten days of paralysis ultimate recovery can be assured Nerve palsies may appear at any time from the first to the ninth week of the disease Paralysis of the palate occurs earlier than other types of involvement which rarely develop before the third week

DIAGNOSIS

The diagnosis of diphtheria and the decision to give or withhold antitoxin must rest in large measure on clinical judgment *Smears* taken from the membrane stained with Loeffler s methylene blue and examined directly are of great help if positive but if negative by no means exclude the disease *Cultures* should be taken whenever there is the slightest suspicion of a membranous inflammation or exudate The culture must be made with care using a good light and making certain that the swab

very rare It is ent ely pre entable by rigid sterile technic in the preparation of suture material Tetanus may follow *vaccination* and it sometimes follows *self induced abortions* Finally there are cases which must be listed as *idiopathic* since the mode of introduction of the organism into the tissues is unknown

Pathogenes s —The introduction of tetanus spores into the tissues of a normal animal is not suffic ent to produce clinical evidences of toxemia The development of the d sease re quires that the injected area be traumatized since local necros s of tissue must be present before the spores will germinate and produce toxin An environment favorable for the growth of the organism and *the elaboration of toxin is provided by d rect trauma of tissues* the presence of foreign bodies in the wound the symbiotic growth of other bacteria especially other anaerobes and the necrotizing effect of soluble calcium salts in the wound It requires the introduction of very few spores given optimal conditions to produce clinical tetanus

Tetanus *tox n* has an affinity for nervous tissue and myoneural junctions Once toxin reaches the nerve cells it cannot be neutral zed by the administration of antitoxin hence the *ea l y* admin stration of antitoxin in large amounts is essential in therapy The route of dis eminat on of the toxin from the local site is still disputed The toxin may travel up the *axis cyl nders of peripheral nerves to reach the anterior horn cells of the spinal cord or lymphat c and blood stream dissem nat on* may occur with later absorption of toxin by the nerve cells of the cord and br n

Clinical Manifestations

In the majority of patients the *incubation period* of tetanus approx imates seven days although the administration of a dose of antitoxin too small to prevent the disease may prolong this span The early manifesta tions are not striking or characteristic There is usually a history of a wound of variable degree which may be healed completely by the time symptoms develop The complaints in the early stages of muscle spasm include restlessness insomnia headache or irritability followed by sore-ness or stiffness of the muscles of the jaws neck pharynx back abdom inal wall and extremities

Following *the nondescript premonitory phase the characteristic syn* drome develops rapidly *Trismus* and the *risus sardonicus* result from spasm of the facial muscles and *difficulty in swallowing* is caused by the spasm of the pharyngeal muscles Later there develop *inability to open the jaws cervical rigidity opisthotonos* and generalized persistent *spas ticity* of the muscles of the trunk and extremities The abdomen may be board like Urinary suppression and constipation are secondary results of *spasm of the sphincters*

Superimposed on this persistent spasticity and rigidity acute tonic *convulsions* of variable intensity seize the patient at irregular intervals The mind remains clear and the temperature is usually normal but any stimulus such as a loud noise or rough handling may set off a mass stimu lation of muscles producing a generalized *tetanic seizure* If the intercostal muscles diaphragm or glottis are involved in tonic spasm respiration is obstructed an intense cyanosis is observed and death may result from *acute respiratory arrest* If the patient survives the first few days of seizures he may die later of *aspiration pneumonitis* which commonly re-sults from efforts to suck in air

Diagnosis

It is extremely difficult to make a bacteriological diagnosis of tetanus *The organism is fastidious* in its growth requirements and must be cul tured under strict anaerobic conditions Blood cultures are sterile Failure to recover the bacillus does not invalidate the clinical diagnosis

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In fulminating cases death from toxic myocarditis may occur suddenly and with little warning during the first week of the disease Much more commonly, however symptoms of myocardial and circulatory involvement develop during the second week of the disease and they may not appear until the third or fourth weeks

With myocardial involvement the pulse becomes rapid and weak and the blood pressure falls The muscular quality of the first heart sound is lost *Arrhythmias* particularly partial or complete *heart block* (p 819) are encountered When involvement of the myocardium is less extensive the only abnormality may be a prolongation of the P-R interval or inversion of the T waves in Leads I and II

The *prognosis* in the presence of myocarditis should be guarded If the patient survives for a week or ten days recovery is anticipated but prolonged and complete bed rest is indicated

NEURITIS

Paralysis as a result of toxic neuritis is one of the most important sequels of diphtheria occurring in from 5 to 20 per cent of all hospitalized patients The muscles of the *soft palate* are generally first affected and may be the only ones involved It will be noted that the voice has become nasal in quality and the uvula can be seen to hang limp The *pharyngeal muscles* also may be involved leading to difficulty in swallowing and regurgitation of food and fluids through the nose The *extra ocular muscles* are not uncommonly affected causing *strabismus* and *diplopia*

At times the muscles of the *neck trunk* and *extremities* become paralyzed and in rare cases, the *phrenic nerve* is involved resulting in respiratory distress If both the diaphragm and intercostal muscles are affected death may result from asphyxia

The *prognosis* of the neuritides as far as return of function is concerned is excellent so that if the patient can be tided over the critical week or ten days of paralysis ultimate recovery can be assured Nerve palsies may appear at any time from the first to the ninth week of the disease Paralysis of the palate occurs earlier than other types of involvement which rarely develop before the third week

DIAGNOSIS

The diagnosis of diphtheria and the decision to give or withhold antitoxin must rest in large measure on clinical judgment *Smears* taken from the membrane stained with Loeffler s methylene blue and examined directly are of great help if positive but if negative by no means exclude the disease *Cultures* should be taken whenever there is the slightest suspicion of a membranous inflammation or exudate The culture must be made with care, using a good light and making certain that the swab

Reactions to alum precipitated toxoid are not especially severe A *hard nodule* forms under the skin and may persist for one or two weeks but it is of little consequence Children exhibit little or no reaction to subcutaneous or intramuscular injection Older patients may have local swelling and soreness but constitutional symptoms of any severity are uncommon Allergic reactions may result from substances present in the medium in which the toxin is produced Hence it may be wise to perform an intradermal test for sensitivity before giving the second injection of toxoid

Combined Treatment—It is now the practice to immunize children with *combined diphtheria and tetanus toxoid* Antitoxic response to both antigens is as satisfactory by the combined method as to either antigen used alone Combined diphtheria and tetanus alum precipitated toxoid is given subcutaneously in 2 doses of 1 cc each at intervals of six weeks to three months There is much to recommend this practice since the protection against two diseases is insured at the same time and with no extra effort or additional injections The addition of 20 billion pertussis organisms to the mixture provides triple benefits at the cost of slightly increased reactivity

Passive Immunization—The prophylactic administration of *tetanus antitoxin* proved its worth conclusively in World War I when the incidence of tetanus was remarkably reduced on the western front It is impossible to lay down categorical rules as to which wounds are potentially infected with tetanus spores In general *compound fractures deeply lacerated wounds and puncture wounds contaminated by soil and manure should be treated by the prophylactic administration of 500 to 1500 units of tetanus antitoxin The serum is given intramuscularly as near the site of the wound as possible* Preliminary tests for sensitivity are required (p 86) and surgical cleansing of the wound is essential as described elsewhere (p 39 8)

ACTIVE SPECIFIC TREATMENT USING ANTITOXIN

In contrast to the proven efficacy of antitoxin in the prevention of tetanus it is difficult to prove in any conclusive fashion that antiserum is of significant value in the active treatment of clinical tetanus Despite the reasonable doubt that exists as to its benefits the physician is required to inject antitoxin as soon as the diagnosis of tetanus is certain or even probable

Dosage—The proper dosage of Tetanus Antitoxin U S P is controversial but it is wiser to force treatment than to regret any possible inadequacy Cumulative experience indicates that a total dose of 60 000 to 100 000 units should be given particularly to patients with severe infections whose incubation period is less than six days The dosage should be the same for children as adults regardless of body weight As a practical precaution the practitioner should insist on an antitoxin whose date of issue was a year ago or less and one which has been kept in an icebox during that time Combined Tetanus Gas Gangrene Antitoxin N N R is recommended for complicated infections

Route of Administration—Controversy also exists as to the route of administration of serum The weight of evidence appears to be against the use of intrathecal injections It is now generally accepted that toxin reaches the nervous system by way of the blood stream and it is unwise under

due to hypersensitivity to bacterial proteins To detect these sensitive individuals the *Maloney test* has been devised It consists of the injection of 0 1 cc of a 1 20 dilution of toxoid to be used as a control in the Schick test instead of the heated toxin

Patients with a positive Maloney test are given three doses of toxoid beginning with 0 25 cc or three doses of toxin antitoxin using 1 0 cc at intervals of two weeks Three to six months after any type of immunization a Schick test should be done to determine whether immunization has been successful If the reaction is positive another injection of toxoid or toxin antitoxin is required

Alum Precipitated Toxoid —In 1926 *alum precipitated toxoid* was prepared by precipitating fluid toxoid with alum separating and washing the precipitate and resuspending it in saline *This preparation appears to be the most potent for active immunization* It was hoped originally that a single subcutaneous injection of 1 0 cc would provide sufficient antigenic stimulation to produce active immunity and to a large extent this is probably true Nevertheless for best results two injections of 1 0 cc with an interval of one month between doses is recommended This is the indicated procedure for children under the age of twelve and older children or adults with a negative Maloney test

Immunization to diphtheria should be begun before the end of the first year preferably when the child is about nine months old A Schick test should be done on entering school and if positive immunization is repeated A combination diphtheria tetanus toxoid is commercially available and protects against both diseases The addition of 20 billion pertussis bacilli per cubic centimeter gives protection also against whooping cough

PASSIVE IMMUNIZATION

The intramuscular injection of a sufficient dosage of diphtheria antitoxin protects most individuals exposed to the disease for three to four weeks The usual amount is 500 units for infants 1000 to 2000 units for children and 2000 to 3000 units for adults

Passive immunization is used but little at the present time except for heavily exposed individuals known to be susceptible Whenever possible contacts should have nose and throat cultures taken and Schick tests done These can be read provisionally in twenty four to forty eight hours Antitoxin is administered only to those definitely exposed persons who have a positive nose or throat culture and a positive Schick test Those with positive cultures and negative Schick tests need not receive passive immunization Each person with a positive culture regardless of antitoxin injection is isolated until cultures are negative or the organism is proven to be avirulent (p 303)

ANTITOXIN

In the *active specific treatment* of diphtheria the most important principle is the prompt administration of antitoxin in adequate dosage The overall mortality of cases treated on the first day of illness is less than 3 per cent while if antitoxin is delayed until the fourth day, the mortality is often as high as 25 per cent

When the clinical diagnosis is suspected Diphtheria Antitoxin U S P should be given immediately without waiting for laboratory confirmation

cause less restlessness and discomfort than subcutaneous hypodermoclyses *Convulsions* must be treated vigorously and promptly with sedatives (p 1518) If *cyanosis* develops during convulsions its cause should be determined If it is due to muscle spasm sedation is indicated but if due to pharyngeal obstruction from food or secretions suction is required If *pharyngeal spasm* is unrelieved by sedation *tracheotomy* may be necessary *Aspiration pneumonia* may be prevented by careful oral hygiene the use of suction and frequent change of position

SEDATION

Adequate sedation is the key to the successful treatment of tetanus It is required before the administration of antitoxin the institution of surgical procedures and manipulation or moving of the patient Emergency sedation is demanded in the presence of convulsions since the latter may cause death by asphyxia facilitate the development of aspiration pneumonitis or produce compression fractures of the vertebrae

The objective of sedation is the control of rigidity and convulsions by the maintenance of a state of light to moderate narcosis Yet it is mandatory to preserve the cough reflex in order to prevent aspiration pneumonia The sedative drugs may be given by mouth by rectum by intramuscular or intravenous injection Inhalation anesthesia is to be avoided if possible

By the oral route, the patient may receive chloral hydrate or one of the barbiturates such as *sodium amytal* The former is ordered in dosages of 1 to 2 gm (15 to 30 grains) with a double quantity of *sodium bromide* as in the familiar bromide and chloral prescription (p 1487) The sodium amytal capsules are administered in double the hypnotic doses The repetition of these drugs depends upon their efficacy and the reaction of the patient

Rectal sedation employs *avertin with amylene hydrate* using an average initial dose of 25 milligrams per kilo or *paraldehyde* 15 to 30 cc in a two-ounce starch paste The avertin dosage is doubled if convulsions have occurred and the paraldehyde being rapidly excreted is repeated within thirty to sixty minutes

For *intramuscular injection* the 10 to 20 per cent aqueous solution of *sodium amytal* is best employed The initial dose is approximately 5 mg per kilo of body weight with an upper limit for total dosage of 240 mg (4 grains) for children and 480 mg (8 grains) for adults

Intravenous anesthesia is required in patients who cannot be controlled by the oral rectal or intramuscular injections and for those who are having active convulsions If an intravenous drip has been set up for the injection of antitoxin the sedative drug is easily alternated with the biological product or injected slowly into the rubber tubing just above the connecting piece that attaches to the needle (p 3776) For rapid effect *sodium pentothal* is to be preferred though *paraldehyde* has its advocates

Our preference in a patient who has not had convulsions favors the oral use of chloral hydrate with sodium bromide Should this mixture prove ineffectual the next step involves the rectal administration of avertin or paraldehyde or the intramuscular injection of the sodium amytal With convulsions an intravenous drip is set up for the administration of anti

If botulism organisms or spores are eaten fresh they produce no damage However if foods are canned or preserved by methods which do not kill the spores the latter may germinate and form toxin When contaminated food is ingested the clinical syndrome of botulism results

Toxin Formation —Botulinum toxin is thermolabile and is destroyed by heating to 65 to 80 C for thirty minutes As a result, the heating of contaminated home preserved foods before use renders them nontoxic Unlike the toxin of diphtheria and tetanus botulinum toxin is not destroyed by the gastric juice but passes unaltered through the stomach and is then absorbed by the intestinal mucous membrane

There have been recognized at least five types of botulinum toxins Toxins A and B are responsible for the majority of human cases of botulism while the other toxins produce the disease in the lower animals Each of the toxins is antigenic and capable of stimulating the production of a *specific antitoxin* Horses can be immunized and a *polyvalent antitoxin* is available for treatment and prophylaxis

Botulinum toxin is one of the most powerful poisons known to medicine It is estimated that the ingestion of as little as 0 01 mg may cause a human fatality Clinical observation verifies this in that very little of the infected food need be ingested in order to produce severe symptoms

Clinical Manifestations

The *incubation period* of botulism varies from twelve to thirty six hours The symptoms begin with weakness and dizziness and are soon followed by signs of *cranial nerve paralysis Strabismus* and *ptosis of the lids* due to paralysis or weakness of the extraocular muscles *difficulty in swallowing palatal paralysis aphonia* and *respiratory difficulty* may occur There are no sensory disturbances and the mind remains clear until delirium or coma sets in shortly before death Gastro intestinal symptoms are mild and inconspicuous There is likely to be some vomiting and constipation but colic and diarrhea are absent The temperature remains normal or subnormal Death results from respiratory failure or from aspiration pneumonia

Diagnosis

The diagnosis of botulism is difficult chiefly because the disease is so rare that the possibility of its presence does not occur to the practitioner Gastro intestinal symptoms are not prominent so that the thought of food poisoning is rarely considered

The acute development of a motor paralysis particularly involving the cranial nerves of an afebrile patient should suggest the possibility of botulism If a number of similar instances occur in individuals who have ingested the same food the diagnosis is almost certainly established

While there is no definitive laboratory aid in the establishment of the clinical diagnosis so far as the patient is concerned evidence may be obtained from *analysis of the suspected food* The can from which the edible was obtained should be stored on ice until it can be brought to the laboratory Its contents are injected intraperitoneally into guinea pigs Half of the animals are protected by previous injection with antitoxin while the remainder receive the food product alone If death results in the unprotected animals and not in those who have received antitoxin the diagnosis is established The stools of the patient may contain *Clostridium botulinum* but the isolation of the organism is exceedingly difficult and its presence does not necessarily establish a diagnosis

See *Differential Diagnosis of Food Poisonings* (p 240)

tions are *Gas Gangrene Antitoxin N N R* which contains the immunity substances against *Cl perfringens (welchii)* and *Cl septicum* and *Polyvalent Gas Gangrene Antitoxin N N.R* which is obtained by additional immunization against *Cl novyi (oedematiens) Cl bifermentans (sordellii)* and *Cl histolyticum* The most practical product however is the *tetanus gas gangrene antitoxin* which protects against tetanus perfringens and septicum This horse serum is given in a dose of 1500 units of tetanus antitoxin and 2000 units of the clostridia for prophylaxis larger doses are used for active treatment

ACTIVE TREATMENT

The active treatment of a clinical gas gangrene infection requires a coordinated attack by the administration of antitoxin and the anti infective agents by surgical intervention and occasionally by irradiation therapy

Antitoxin—Either polyvalent or mixed *tetanus gas gangrene antitoxin* is utilized by intravenous injection in large doses In point of fact it is good practice to set up an intravenous drip so that relatively massive doses of serum may be employed in addition to the anti infective agents

Anti infective Agents—Though there are both favorable and unfavorable reports concerning the action of the *sulfonamides* on clostridia there is very little doubt as to the marked susceptibility of these organisms to *penicillin* The severity and high fatality rate of gas gangrene make it imperative for the practitioner to utilize every agency that is at his disposal We favor the use of serum sulfonamide and penicillin in the manner indicated a *continuous intravenous drip* is instituted in order to deliver at least 100 000 units of *antitoxin* in the course of twenty four hours The sulfonamides are given orally with an initial dose of 6 gm of *sulfadiazine* or intravenously as 100 cc of 5 per cent *sodium sulfadiazine* subsequent oral doses of 1 gm are given every four hours *Penicillin* is injected intramuscularly employing an initial dose of 100 000 units and 25 to 50 000 units are given at three hour intervals thereafter Penicillin may be alternated in the intravenous drip with serum under which circumstance a solution is prepared so that each cubic centimeter of the infusate contains at least 500 units of the antibiotic in this way a twenty four hour delivery of 2000 cc of the infusate affords a dosage of at least 1 000 000 units of penicillin If the patient is severely ill the priming dose of 50 to 100 000 units may be injected immediately after the drip has been set up

In overwhelming protracted or seemingly resistant infection especially in the weakened the aged and the very young high concentrations of penicillin effected by massive daily doses of 500 000 to 2 000 000 units or by the production of blockade (p 109) are worthy of earnest consideration

The anti infective agents are also of value by topical application powdered *sulfanilamide* is placed in the depths of the wound or a solution of *penicillin* 250 units to the cubic centimeter is locally applied

Surgery—Despite the phenomenal results of anti infective therapy the practitioner cannot afford to neglect the local wound The area is widely excised and debrided local applications of sulfanilamide powder or penicillin are made into the depths of the wound while the systemic program is being pursued

CHAPTER 10

BACILLARY INFECTIONS BRUCELLAE AND PASTEURELLEAE

Brucellosis (*Br melitensis*)
Plague (*P pestis*)
Tularemia (*P tularensis*)

BRUCELLOSIS (MELITENSIS UNDULANT FEVER MALTA FEVER BANG S DISEASE MEDITERRANEAN FEVER GOAT FEVER TEXAS FEVER RIO GRANDE FEVER)

BRUCELLOSIS is an infectious disease of goats cattle swine and other domestic and wild animals Man is infected by contact with diseased animals or by the drinking of unpasteurized milk *Whereas brucellosis was regarded previously as a rare clinical entity it is becoming increasingly evident that the disease is a public health problem of major importance*

Brucellosis is apparently widespread in this country and is an important cause of chronic ill health Its manifestations are protean and bizarre and the criteria for diagnosis are unsatisfactory and inaccurate As a result it is probable that a large number of patients with acute and chronic brucellosis are not recognized Those likely to be infected include farmers veterinarians dairymen butchers meat packers and all who drink raw milk

Varieties—The recognized varieties of brucella are the caprine bovine and porcine strains which are closely related but may be differentiated by *agglutinin absorption* by the varying bacteriostatic action of certain dyes by glucose utilization and other differences in metabolism

The *caprine or goat variety* is responsible for *Malta fever* Man contracts this disease by drinking raw goat s milk or by contact with sick animals This form is rare in the United States but common on the Isle of Malta *Brucella abortus or the bovine strain* causes *infectious abortion* in cattle (*Bang s disease*) This infection is transmitted to man chiefly in the medium of *raw milk* and is the most commonly observed variety in the United States *Brucella suis or the porcine type* produces disease in *swine*, and in man who is probably infected by handling the *meat of infected animals*

Bacteriology—The Brucella organisms are small *gram-negative* cocco-bacilli which are difficult to grow except under exacting conditions Huddleston s liver infusion broth is the most favorable medium *Br suis* and *Br melitensis* grow under ordinary atmospheric conditions but *Br abortus* requires an atmosphere containing 10 per cent of carbon dioxide In blood cultures the organisms grow very slowly and the flasks should be incubated for at least three weeks before concluding that they are sterile

CLINICAL MANIFESTATIONS

The clinical picture of brucellosis is varied complex and vague Acute and chronic forms of the disease exist and will be separately considered

ACUTE BRUCELLOSIS

Acute brucellosis is initiated by an *incubation period* which is followed by a *septicemic* or *typhoidal state* This latter may be succeeded by recov

chains of streptococci Many of the bacilli show oval bodies (*Babes Ernst g nules*) situated ar one or both ends of the cell See Fig 43

The d phtheria bacillus is *nonmot le* and *aerob c* On Loeffler s media of coagulated beef rum and infusion broth the organisms grow especially well outstripping contaminants and appearing in twelve to twenty four hours as grayish white glistening colonies It is often possible to obtain sufficient growth to make smears in which the organisms can be identified fter but four to e ght hours of incubation A medium of onsiderable value is cyst ne tel lurite aga Iotassium tellu ite incorpo ated in agar has the p operty of coloring diphtheria olonies gray to slat black wh le most other organ sms remain uncolored This p operty akes it possible to p ck out diphtheria colon es from mi ed cultures wh ch hav few d ph theria organisms and many contaminants

After is l tion of a suspected o gan sm in pure culture *fermentation eact ons* ar t l d In serum w t or nfusion broth co ta ing variou arboh drates *C diphtheri*



Fig 44 — Tons lla and uvular diphtheri

ferm nts dextros and malto e but not saccha os *C h ffm* ferments n ne of th se th ee uga s while *C xerose* ferments all f th m

Toxin P oduct on and V rulence — Diphtheria *t xin* is a true exotoxin prese t in the filtrates of b oth cultur s of v rulent d phtheria bacill It is generally prepared by inocu lating o ganisms into broth m d a shallow layers and then obtaining the bacter a fre filtrates after incubat on for a week The toxin is subsequently refined and conc ntrated It s r dly d st oyed by heating at 60 C and its exact chemical compositio s still un known although it appears to be p otein in n ture Rec ntly it h s been found possible t produce toxin of high potency on chemically d fined med Such to in has the advantag of bei g f ee f m impurities and al n ub tance p esent in broth

Not all strains of *C d phtheriae* p duce tox Since avirulent a d virulent strain may be morphologically and culturally id nt c l each o ganism must be tested for its *toxin producing* capacity an l t rulence for lat to v n mals If gu i p g is njected sub-

Courtesy of P rke Dav Company

the gallbladder or *chronic cholecystitis* during the course of the acute illness or appearing months or years after the original febrile episode has subsided and been all but forgotten

Respiratory Manifestations —*Cough* is a common symptom in brucellosis during the acute febrile stage In most instances it is a manifestation of a *bronchitis* but some patients show evidences of *pneumonitis* or a scattered *infiltration* not unlike that seen in tuberculosis or the primary atypical pneumonias of unknown etiology (p 400)

See *Differential Diagnosis of Commoner Febrile Skeletal Disturbances* (p 192)

Other Manifestations —On rare occasions brucellosis may produce an *endocarditis* with localization of the organisms on heart valves that have been previously damaged by rheumatic fever or congenital defects Finally the lesion of brucellosis may be manifest in the genito urinary tract giving rise to *orchitis* or *epididymitis* In the female there have been isolated reports of involvement of the *adnexa*

CHRONIC BRUCELLOSIS

Chronic brucellosis may give rise to a wide range of symptoms Only a small number of the patients give a history of a previous febrile illness that suggests the acute phase of brucellosis Most patients have had an *ambulatory disturbance* with vague symptoms such as weakness exhaustion low grade and intermittent fever and easy fatigability Many of these individuals are considered *neurasthenics* (p 1350) since meticulous physical examination and exhaustive diagnostic laboratory tests are often inconclusive or completely negative

Chronic brucellosis is characterized by periods of *remission* and *febrile exacerbations* without localizing manifestations in any organ of the body Those who have studied this disease most carefully believe that chronic brucellosis is the most likely cause of many of the baffling fevers and complaints of unknown origin that are so frequently encountered in clinical practice

DIAGNOSIS

The diagnosis of brucellosis is most unsatisfactory and difficult A clinical opinion at best is a hazard Laboratory corroboration is difficult to obtain and with the exception of the positive identification of the organism complex and uncertain in its interpretation At the present time the diagnostic problem is beyond the technical possibilities of the practitioner who should seek assistance from the special consultants of the United States Public Health Service

The clinical diagnosis of brucellosis should be suspected any time that there is an obscure illness in patients who drink raw milk or have contact with animal tissue that may possibly be infected This category includes farmers veterinarians meat packers butchers and those who live in a household where raw milk is obtained from a single cow or a small herd

The diagnosis of brucellosis will be made more often where there is a high index of suspicion It will never be encountered by the practitioner who adheres to the older narrow concept of a febrile disease occurring

chains of streptococci Many of the bacilli show oval bodies (*Babes Ernst granules*) situated near one or both ends of the cell See Fig 45

The diphtheria bacillus is *nonmotile* and *aerobic* On Loeffler's *media* of coagulated beef serum and infusion broth the organisms grow especially well outstripping contaminants and appearing in twelve to twenty four hours as grayish white glistening colonies It is often possible to obtain sufficient growth to make smears in which the organisms can be identified after but four to eight hours of incubation A medium of considerable value is cystine tellurite agar Potassium tellurite incorporated in agar has the property of coloring diphtheria colonies gray to slate black while most other organisms remain uncolored This property makes it possible to pick out diphtheria colonies from mixed cultures which have few diphtheria organisms and many contaminants

After isolation of a suspected organism in pure culture *fermentation reactions* are studied In serum water or infusion broth containing various carbohydrates *C diphtheria*



Fig 44 —Tonsillar and uvular diphtheria

ferments dextrose and maltose but not saccharose *C hoffmanni* ferments none of these three sugars while *C xerose* ferments all of them

Toxin Production and Virulence —Diphtheria *toxin* is a true exotoxin present in the filtrates of broth cultures of virulent diphtheria *bacilli* It is generally prepared by inoculating organisms into broth media in shallow layers and then obtaining the bacteria free filtrates after incubation for a week The toxin is subsequently refined and concentrated It is readily destroyed by heating at 60 C and its exact chemical composition is still unknown although it appears to be protein in nature Recently it has been *found possible* to produce toxin of high potency *on chemically defined media* Such toxin has the advantage of being free from impurities and alien substances *present* in broth

Not all strains of *C diphtheriae* produce toxin Since avirulent and virulent strains may be morphologically and culturally identical each organism must be tested for its *toxin producing capacity* and its *virulence* for laboratory animals If a guinea pig is injected sub

Courtesy of Parke Davis Company

exception however *the negative test* rules out brucellosis except in the early septicemic phase

Opsonophagocytic Test—The opsonophagocytic test requires that 01 cc of the patient s blood be mixed with an equal volume of a suspension

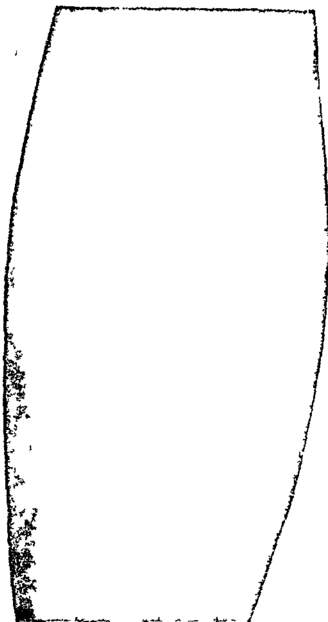


Fig 45—Brucellergin skin reaction *

of organisms The mixture is incubated for thirty minutes and then stained after which the numbers of the organisms ingested by the leukocytes are recorded The greater the number of phagocyted organisms the higher is the opsonic index of the patient s blood The test is difficult of evaluation

Huddleson Brucellosis in Man and Animals Commonwealth Fund New York

y ars of age although in recent years a tendency has been noted for infections to occur in older children and adults

The disease is transmitted as are respiratory diseases in general by *droplet infection* from the upper respiratory tract of one individual directly or indirectly to another Fomites have occasionally served as the source of infection Epidem cs due to the consumption of contaminated raw milk have occurred from time to time

The *communicabil ty* of diphtheria is not to be compared with m asles whooping cough or influenza but the attack rates are highest among susceptible family contacts of frank cases The reservoirs of infection are the patient convalescent and *healthy carriers* The convalescent carrier is of little risk to the community because his status is known and con trol measures are carried out which l mit his ability to spread infection The most im portant factors in the dissemination of the disease are healthy carriers the majority of whom are not infected with virulent stra ns The incidence of carriers varies widely according to the density of populati n and the latitude At the present time the hi hest carrier rates in this country are in the southern states where 1 or 2 per cent of normal persons carry v rulent organisms In some northern states the percentage of carriers of toxogenic strains in the general population is as low as 0.- per cent

Immunity—In dipl theria infectivity depends upon the prevalence of the organism in the environment and the immunity of the patient The Schick test which offers a con ven ent method of determining the latter factor reveals that *newborn nfants* have pas ive immunity as the result of the placental transfer of antitoxin from the mother This persists for the first six months of l fe and consequently diphtheria is ra e in this age group *From the age of one to three* the majority of children are Schick posit ve and therefore suscep t ble Thereafter susceptib l ty diminishes with increasing ag so that 75 per cent or mo e of adults are Schick negative

There has been some speculation as to whether the development of immunity may not be the re ult of physiological maturat on of the tissues The evidence however is against thi view and indicates that immunization is the result of contact with the organisms in minimal dosage below the level at which clin cal disease results In recent years as a result of the rapid decrea e in the prevalence of d phtheria there has been a shrinkage of the natural reservoir (the carrier) so that the development of natural activ immunity is being postponed to later ag groups For example in a recent survey in Alabama whe e both cases and carriers are still relatively preval nt 70 per cent of ch ldren from five to nine years of age were Sch ck n gative (im nun) On the other hand in Kingston New Yo k where cases have been rare for ma y years and carriers are few only 17 per cent of the children in this age group we e Schick n gative This trend implies that there is diminishing oppor tunity to develop natural active immunity to diphther a and emphasizes the necessity for *routine active immuni ation* of all children Unless this is done it is entirely possible for d phtheria to a am assume epidemic proportions in a population unprotected by naturally acquired immunity

Pathology—D phtheria is primarily a local infection of a mucous membrane asso iated with a to emia due to the systemic abso ption of toxin produced by the organisms at the site of the l sion The patholo y of the d sease including the formation of the membrane i the result of the a t on of diphther a toxin The organ sms themselves have no invas e pow r and s pt cem a do not occu ex ept pos bly terminally

Toxin causes the death of the cells of superficial layers of the pharyngeal mucosa Tl ere is tl en a deposit on of fibrin and c llular exudate on the surface This together with the oagulat on nec osis of t ssue re ults in the formation of the membrane in whose *de per* lay rs are the dipl the a bacilli

The syst mic ab rptio i of t xin produces fatty degenerat on of the muscle fibers of the *myoc d um* with dema hyaline degene ation and interstitial fibrosis In the *periphe al motor and senso y erves* fatty degen ration of the myelin sheaths is ob erved The *spleen* is swollen a d de ply cong te l Deg nerative changes and swelling occur in the *lymph odes* particularly those n the anter or cervical triangle Areas of necrosis in the *l ier are* obs rv l at autopsy althou h jaund ce is not seen Cloudy swell n and at times frank ephrotic les ons ar found in the kidneys *Adrenal necrosis* may account for the fall in blood p e u e s n in very tox c pat nts *L ukocytosis* is generally present and in addition *seve e* grades of *anemia* may be encount red Experimentally the enti e pathological picture of i phth ria with the xception of the membrane may l e reproduced in susceptible an mals by the parenteral injection of toxin

where there is involvement of the brain heart or lungs It is not indicated in the chronic stages of the disease The suggested dose is 20 to 30 cc given daily into the muscles or veins for 5 or 6 doses

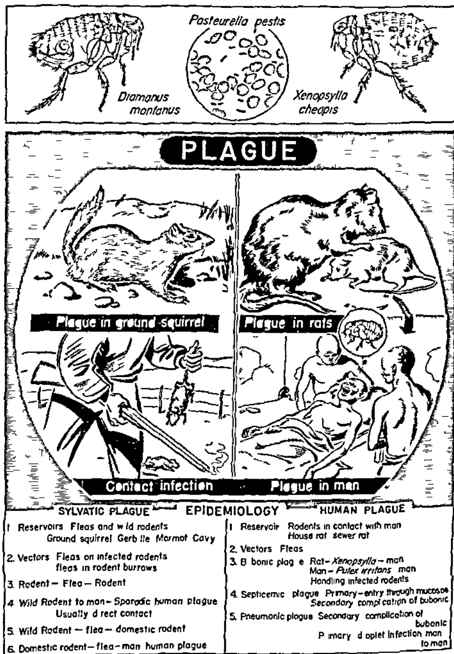


Fig 46 — Epidemiology of plague *

Convalescent Serum — Convalescent serum from recently recovered patients has been employed and there have been some favorable reports which are difficult of evaluation The use of convalescent serum has the

* Mackie Hunter and Worth Manual of Tropical Medicine

lowing begin to subside The administration of antitoxin does not prevent this evolution of the local lesion but hastens its disappearance

LARYNGEAL TYPE

The larynx may be involved by the downward spread of the pharyngeal membrane or it may be affected primarily In the latter case the *onset is indistinguishable from a simple catarrhal inflammation* It begins with *hoarseness* slight *stridor* and moderate elevation of temperature The local and constitutional symptoms steadily increase in severity until characteristically the *voice is lost* entirely *Dyspnea* increases progressively and by the end of the first twenty four hours breathing is loud and stridulous indicating obstruction to inspiration and expiration The accessory *muscles of respiration are called into play* *cyanosis* becomes evident about the fingertips or lips and *tachycardia* becomes marked If unrelieved death from suffocation may occur especially in infants in from thirty six to forty eight hours In children from two to five years of age in whom laryngeal diphtheria is most commonly seen the progress of the disease is somewhat slower and less fulminating Death may occur from pulmonary complications especially pneumonitis

In the laryngeal form of disease the symptoms are mainly the result of mechanical obstruction and its sequels The size of the membrane is such that large amounts of toxin are not absorbed consequently toxic manifestations of the disease myocarditis and nerve paralysis are not frequent

NASAL TYPE

Primary nasal diphtheria is quite uncommon and is most likely to occur in infants and young children Constitutional symptoms are almost entirely lacking There is usually a persistent purulent or bloody unilateral or bilateral *nasal discharge* which may last for several weeks before its true nature is recognized There is generally excoriation about the nostrils

From the standpoint of the patient nasal diphtheria is a *benign disease* but it is particularly important from the public health viewpoint because so often it goes unrecognized and thus serves as a source for the further dissemination of bacilli

SEPTIC TYPE

Fortunately the septic type of diphtheria in which *hemolytic streptococcal infection* is associated with or superimposed on diphtheria is rare The symptoms are acute from the onset with *high fever extensive membranes* and marked swelling of the tissues of the neck In a considerable proportion of such cases *toxic myocarditis* and *hemolytic streptococcal septicemia* are likely to develop

SKIN DIPHTHERIA

In rare instances diphtheria may occur on the skin or mucous membranes following the direct inoculations of organisms into wounds Other areas which may be involved are the conjunctivae ears and vulva

COMPLICATIONS AND SEQUELS

The milder nasal and tonsillar forms of diphtheria may be associated with *otitis media* or *peritonsillar abscess* but severe complications such as

Clinical Manifestations

Plague manifests itself as an overwhelming septicemia but less virulent forms involve the lymphatics or the lungs

Plague Septicemia —The septicemic type of plague is usually a massive invasion of the blood stream with death before there is time for local bubo or pulmonic localization The diagnosis is suspected in the presence of an epidemic

Bubonic Plague (Black Death)—The common clinical type of plague is the bubonic form This is characterized by the development of *acute painful lymphadenitis* usually of the *inguinal nodes* It is quickly followed by a septicemia producing petechial hemorrhages (the *Black Death*) toxemia and high fever Recovery may occur by lysis but the mortality in different epidemics varies from 30 to 75 per cent

A variety of bubonic plague is termed *pestis minor* a mild ambulatory disease with little or no toxemia

Pneumonic Plague —The *pneumonic type* (p 2192) of plague is almost invariably fatal The sputum is loaded with plague bacilli and direct transmission of organisms from man to man is readily accomplished

Diagnosis

In the presence of an epidemic the diagnosis of plague is made on the basis of epidemiologic data More definitive information is afforded by the demonstration of bipolar pleomorphic bacilli from inguinal aspirate pus or sputum Application of infected material to the scarified abdomen of a guinea pig results in fatal septicemia with hemorrhagic lesions in three to five days

See *Differential Diagnosis of Commoner Febrile Skeletal Disorders* (p 192)

Treatment

Active Immunization —Active immunization has been attempted in plague using living attenuated cultures or heat and phenol killed organisms *Plague Bacillus Vaccine N.N.R* contains 2000 billion killed organisms per cubic centimeter and is injected in an initial dose of 0.5 cc followed by two or three subsequent doses of 1 cc A booster dose is added every six months when necessary The reaction tends to be moderately severe at the site of injection but the vaccine appears to have definite value in the prevention of the disease and the lowering of the case fatality rate

Antiplague Serum —An unofficial antiplague serum is available and those who deal with the disease apparently have some confidence in its efficacy Doses of 20 cc may be given subcutaneously intramuscularly or intravenously with repetitions at six hour intervals

Anti infective Agents —There is no evidence that *penicillin* has any deleterious effect on the plague bacillus However there are clinical reports of the efficacy of the *sulfonamides* Using sulfapyridine and sulfathiazole the case fatality rate in a plague epidemic in India fell from 95 per cent in the controlled group to 40 per cent in the sulfonamide treated patients While we have no experience with this dreaded disturbance it would seem from the literature that the high case fatality rate would warrant combined treatment with a continuous intravenous drip alternately delivering antiplague serum and a soluble sulfonamide such as sodium sulfadiazine

comes in contact with the deeper portions of the membrane Swabs should be carefully streaked on Loeffler s serum slants and kept in the vest pocket or in an incubator until brought to the laboratory

Among conditions commonly confused with diphtheria are acute tonsillitis and streptococcic sore throat scarlet fever Vincent s angina and catarrhal laryngitis *Acute tonsillitis* is characterized by abrupt onset with high fever and an exudate on the tonsils which is follicular rather than membranous *Streptococcic sore throat* and *scarlet fever* before the eruption of the rash are also marked by more acute onset and higher fever The throat is diffusely hyperemic and bright red Exudate is rarely as extensive as in diphtheria and it is thinner and more easily removed In *Vincent s angina* the onset is insidious and the temperature not especially high The distinguishing characteristic of the lesion of this disease is the ulceration of the mucous membrane When the diagnosis is in doubt smears commonly reveal fusiform bacilli and spirochetes *Catarrhal laryngitis* may be confused with the laryngeal form of diphtheria especially when the membranes are not present in the nose and throat In nondiphtheritic croup the condition is generally more severe at night and improves during the day The voice is not entirely lost and the symptoms are not progressive

TREATMENT

The treatment of diphtheria represents one of the great triumphs of scientific medicine Prevention is accomplished by active or passive immunization and specific curative treatment by the injection of antitoxin

ACTIVE IMMUNIZATION

Diphtheria may be eradicated by the universal immunization of all children In fact if only 30 per cent of pre school children were successfully immunized widespread epidemics would be unlikely

Toxin Antitoxin—The use of *toxin antitoxin mixtures* for active immunization was suggested by the observation that horses could be immunized with neutral mixtures of toxin and antitoxin The procedure was soon introduced into clinical use largely through the pioneer efforts of William H Park of New York City From 75 to 90 per cent of Schick positive individuals develop Schick immunity in from three to six months after receiving doses of 1 0 cc each by subcutaneous injection The disadvantages of toxin antitoxin are the reactions that occur because of the instability of the mixture and the sensitization to horse serum that may result

Toxoid—In 1923 Ramon found that the addition of formalin to diphtheria toxin rendered the substance nontoxic while its antigenicity was unimpaired This formalin mixture under the name of toxoid quickly found favor because of its stability and its greater antigenic activity together with the fact that it did not induce serum sensitivity From 90 per cent to 98 per cent of Schick positive individuals became Schick negative within three months after the last dose of fluid toxoid Toxoid may be given subcutaneously in two injections of 0.5 cc and 1 0 cc at three week intervals but the best results have followed the use of three doses of 0.5 cc 1 0 cc and 1 0 cc

Plain toxoid is well tolerated by children under six years of age but older children and adults are prone to develop local and systemic reactions

occurs on the *palpebral conjunctiva* It occurs in about 5 per cent of all cases and one or both eyes may be involved Presumably the infectious material is rubbed into the eyes by the fingers Small ulcers develop on the conjunctivae which become markedly inflamed and chemotic There is considerable edema of the eyelids and the surrounding soft tissues *Dacrocystitis* and *panophthalmitis* may develop The regional lymph nodes of the head and neck are affected and may suppurate Despite its evil appearance the eye lesion has a favorable prognosis

Glandular Type—In the glandular type of tularemia which is uncommon there is regional lymphadenopathy but no primary skin lesion

Typhoidal Type—The typhoidal type is the least common and gravest of the varieties of tularemia There is no primary skin lesion or regional lymphadenopathy The patient exhibits prolonged fever and great prostration There is generally a septicemia without localizing signs

Course

Regardless of the portal of entry the course of tularemia is protracted The *acute systemic symptoms* last for two to three weeks during which time there are *repeated chills marked prostration weakness* and *weight loss Fever* is irregular and remittent during this period The *pulse* is rapid and there is *moderate leukocytosis* but *splenomegaly* is not a feature of the disease Nonspecific *cutaneous eruptions* may appear during the course of tularemia usually between the second and fourth week *Morbilliform maculopapular* and *pustular eruptions* have been noted and *erythema multiforme* and *erythema nodosum* also have been observed

Convalescence is slow and it is generally four months to a year before the patient feels completely well and able to return to full activity For many months after recovery from the acute illness there may be periods of low grade fever with weakness and breathlessness on exertion The typhoidal form of tularemia is particularly prone to chronicity

Complications

The common complications of tularemia are suppurative lymphadenitis septicemia and respiratory lesions *Suppuration of involved lymph nodes* is noted in half of all patients with the ulceroglandular form of the infection *Septicemia* probably occurs in the early stages of all types of tularemia and usually disappears when circulating antibodies develop The persistence of septicemia is a grave prognostic sign

In from 15 to 20 per cent of cases of tularemia *pneumonia* or *pleural effusion* develops Pneumonia is present in the majority of patients with the typhoidal type of disease but is a less common feature of the ulceroglandular type It may be the first manifestation of the disease or may develop later in the course The temperature is high while the pulse rate is relatively low and the leukocyte count not above 15 000 per cu mm The course of tularemic pneumonia varies from ten days to several months The overall case mortality rate for the pneumonic type of disease is almost 30 per cent *Pleural effusion* with or without an obvious underlying pneumonitis is a common complication of tularemia The fluid is clear contains a few thousand cells mostly lymphocytes and has a high protein content Unless a history of contact with rabbits is obtained or specific agglutina

The amount of serum to be administered varies with the severity of the infection and with the number of days that have elapsed since the onset. For mild cases with membrane confined to one or both tonsils 10 000 units are adequate for infants under one year of age and 20 000 units for older children. The more extensive the membrane, the larger is the required dose. In cases of moderate severity, where the uvula and nasopharynx are involved, from 40 000 to 60 000 units should be given; the same dosage is indicated for laryngeal diphtheria. The local application of antitoxin to the membrane is valueless.

Antitoxin should be administered in a single dose *intramuscularly* for mild and early cases and *intravenously* for severe and late cases. The usual precautions must be taken for determining sensitivity to horse serum. If the skin test is positive or if there is a definite history of sensitivity, Bovine Antitoxin N N R can be obtained.

The response to antitoxin in adequate amounts is prompt. Within twelve to twenty four hours there is a lessening of toxemia and cessation of spread of the membrane. If these favorable signs are not observed within that time, a second dose of the same or larger size is necessary.

ANTI INFECTIVE THERAPY

The *sulfonamides* are of no value in diphtheria; most experienced clinicians believe that they should be avoided in this condition. The diphtheria organism is sensitive to *penicillin*, however, and there would be no reason why the antibiotic substance should not be given intramuscularly concurrently with *antitoxin*. Under no circumstance should penicillin be given in the place of the serum; if it accomplishes nothing else, it may clear the membranous area of other susceptible organisms and favor healing. Since penicillin has so little threat of toxicity and the ravages of diphtheria may be so severe, it would seem wiser, as in previously described instances, to waste the therapeutic material rather than expose the patient to hazard.

In overwhelming, protracted or seemingly resistant infection, especially in the weakened, the aged and the very young, high concentrations of penicillin effected by massive daily dosages of 500 000 to 1 000 000 units or by the production of blockade (p 109) are worthy of earnest consideration.

LOCAL TREATMENT OF LARYNX

The treatment of laryngeal diphtheria by intubation and tracheotomy is considered elsewhere (p 398).

BOTULISM

Botulism is an intoxication resulting from the ingestion of food which contains the pre formed toxin of *Clostridium botulinum*. The disease, fortunately very rare, is characterized by neuromuscular symptoms and has a high case fatality rate.

Bacteriology.—*Clostridium botulinum* is a gram positive *anaerobic*, *spore forming* organism which is widely distributed in the soil and easily contaminates fruit and vegetables. Botulinum spores are exceedingly resistant and require for their destruction boiling for five hours or autoclaving. An acid reaction in the medium or a high concentration of sugar in preserved food inhibits the formation of toxin, and these principles are utilized in commercial canning, which rarely causes poisoning. *Home preserved foods*, which are more likely to be improperly sterilized, produce most of the clinical difficulties.

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Treatment

The extreme gravity of botulism requires that a careful regulation be enforced in the canning and preserving of food For the most part this is a public health problem Whereas the commercial canning companies can be carefully supervised the instruction of housewives involves considerable difficulty

Technic of Canning and Preserving Food —Housewives are to be taught that *the color odor or taste of food is no indication of the presence of botulinum toxins* Whereas in industry facilities are available for testing and producing an acid reaction in the medium and a high concentration of sugar in the preserved food this cannot be done in the home in consequence of which the housewife must rely on simpler methods These involve the boiling of foods for five hours in order to kill the spores or the heating of preserved edibles for thirty minutes at 65° to 80 C before serving to inactivate preformed toxin

Specific Treatment —A polyvalent *Botulism Antitoxin N.N.R* is available The serum has been used so rarely that it is impossible to evaluate its efficacy To have any demonstrable effect it must be given early and preferably before signs of paralysis have developed Obviously under these circumstances it is only in the presence of an epidemic that the diagnosis would be suspected in the preparalytic phase If there is any reasonable suspicion of botulism antitoxin should be given immediately since the case fatality is so high as to justify the use of heroic measures

In the pre paralytic stage 2500 units of the serum may be injected subcutaneously after paralysis has occurred the dose should be increased to 10 000 units and the injection given by slow intravenous drip

Anti infective Therapy —Whereas there is no evidence that the *sulfonamides* have any effects on clostridia botulinum is sensitive to *penicillin* The antibiotic substance however by no means neutralizes botulinum toxin so that therapy must be conducted by the combined method of administering penicillin intramuscularly and the antitoxin intravenously Again this form of polyvalent therapy is recommended because of the relative gravity of the disease and the proportionately slight risk of the administration of penicillin

In overwhelming protracted or seemingly resistant infection especially in the weakened the aged and the very young high concentrations of penicillin effected by massive daily doses of 500 000 to 1 000 000 units or by the production of blockade (p 109) are worthy of earnest consideration

Prognosis

Botulism is a very serious disease the case fatality rate approximating 60 to 70 per cent The longer the patient survives the better the ultimate prognosis If the patient survives the acute attack ocular palsies may persist for six months or more but eventual complete recovery may be anticipated

incision may be made for drainage but no more extensive revision or excision is wise

Antibiotic therapy with penicillin holds no promise but the clinical reports of sulfonamide treatment are somewhat encouraging Sulfadiazine may be administered in an initial dose of 4 gm (60 grains) and in subsequent doses of 1 gm (15 grains) every four hours thereafter Immediate favorable results have been reported from combined sulfadiazine and serum therapy

The successful introduction of streptomycin treatment in tularemia dwarfs previous accomplishments and promises to replace all other agencies Intramuscular injections of 250 000 to 500 000 units every three hours day and night produce prompt amelioration of symptoms and apparent cure within a few days Injections are continued for several days in convalescence to prevent relapse Serum therapy and sulfonamide supplementation may be reserved for streptomycin failures unless the attack is too severe to hazard procrastination

Prevention

The prevention of tularemia is best accomplished by the education of the public as to the method by which the infection is acquired Those who handle wild rabbits must wear rubber gloves and should receive annual doses of a *vaccine* whose successful use has been reported

ery or *localizing manifestations* in the skeletal nervous digestive respiratory or circulatory systems

Incubation Period.—The incubation period of acute brucellosis varies from a few days to as long as a month Because of the multiplicity of possible exposures and the vagueness of onset it is difficult to determine with any degree of accuracy The initial symptoms resemble those of an ordinary grippe There is gradual onset of weakness and fatigue lassitude chilliness anorexia or constipation Headache generalized malaise arthralgia backache or abdominal pain may be present additionally Cough is an early symptom in approximately one third of all the patients The temperature rises in the afternoon and falls to normal in the morning The febrile rise may be accompanied by chilling or actual chills and the defervescence is attended by profuse sweating

Period of Septicemia.—After a week or so of these vague symptoms the initial diagnosis of grippe becomes untenable and some other infection such as typhoid fever or tuberculosis is suspected The patient is running a fairly sustained *fever* with a *relatively slow pulse rate* and a normal or subnormal leukocyte count A true *leukopenia* is present in half the patients and in others there may be a relative or ab olute *lymphocytosis* The similarity to typhoid is furthered by the presence of a palpable and enlarged *spleen* *Rashes* of a nonspecific nature are frequently seen but there is nothing characteristic in their type or distribution

In contradistinction to the patient with typhoid fever the sufferer from acute brucellosis does not appear as ill as his temperature would indicate He remains mentally alert and clear in contrast to the mental torpor of typhoid

The period of septicemia may last several weeks or several months and usually progresses to a localization of the infection in an end organ as is the case in tuberculosis

See *Differential Diagnosis of Cryptogenic Fevers* (p 26)

Skeletal Manifestations.—*Pains in the muscles and joints* are commonly seen in brucellosis and often there may be observable *peri articular swelling or hydrarthrosis* A common manifestation of brucellosis is *spondylitis* which usually occurs several months after the onset of the febrile illness The vertebral changes may go on to destructive processes or the formation of local abscesses These late lesions may not appear until as long as a year after the original infection leading to considerable difficulty in diagnosis

See *Differential Diagnosis of Commoner Febrile Skeletal Disorders* (p 192)

Neurological Manifestations.—Most patients with brucellosis suffer from *insomnia* and *restlessness* A more tangible complication is a *true meningitis* with a *pleocytosis* in the spinal fluid A considerable number of the deaths recorded from brucellosis occur as the result of this complication *Encephalitis* with headache vomiting focal evidences of brain involvement and papilledema occurs rarely and usually terminates with complete recovery

Digestive Symptoms.—*Abdominal pain* is often so severe and localized as to lead to a laparotomy for a suspected *acute appendicitis* (p 1881) Often the organisms localize specifically in the *gallbladder* just as occurs in typhoid fever There may be a resultant *acute cholecystitis* *empyema of*

BACILLUS MUCOSUS CAPSULATUS (FRIEDLANDER S BACILLUS KLEBSIELLA PNEUMONIAE)

The Friedlander bacillus an occasional cause of pneumonia (p 217l) is sometimes found in normal throats It may produce *otitis media* or *sinusitis* and not infrequently is present in the urinary tract in *pyelitis* and *cystitis*

Friedlander s bacillus is a *gram negative rod* related to the coli aerogenes group It possesses a very large *capsule* and various types are distinguished by differences in the capsular polysaccharide At present, A B C D and an X group of untyped strains are recognized Typing is done by specific serum in a manner exactly similar to the Neufeld typing of pneumococci (p 201) From a practical viewpoint these procedures have no importance since potent therapeutic antiserums are not available

Streptomycin (p 104) gives great promise for specific therapy in the treatment of Klebsiella infections The Friedlander bacillus is resistant to penicillin but strikingly streptomycin sensitive

ERYSIPELOID

The erysipelothrix organisms include *E muriseptica* which causes a fatal septicemia in mice *E rhusiopathiae* producing swine erysipelas and *E erysipeloidis* which is responsible for erysipeloid in man These organisms are gram positive nonmotile nonspore forming short thin bacilli which grow readily on ordinary laboratory media They are probably closely related to one another if not identical and their only importance in clinical medicine is the fact that they may occasionally produce a *localized skin infection* usually on the hands

Erysipeloid occurs most often in those who handle animals fish shell fish or material derived from animals such as hides pelts and bones The disease is also encountered in housewives It is not clear whether fish and shell fish are actually infected with these organisms or whether they are saprophytes passively carried by fish and crustaceans Direct transmission of disease from infected swine to man is uncommon

Penicillin has specific value in the treatment of erysipeloid The antibiotic agent is given parenterally in medium sized doses (p 106)

PYOCYANEUS INFECTIONS

Pseudomonas aeruginosa (*Bacillus pyocyaneus*) is an organism of low virulence When present in wound infections it is generally a secondary invader the most characteristic feature of which is its pigmentary production which gives a *green or blue color to pus* The organism is a slender *gram-negative* rod with polar *flagella* It grows readily on simple laboratory media and forms water soluble bluish green pigment composed of pyocyanin and fluorescin

B pyocyaneus is a not uncommon secondary invader in *chronic suppurative wounds of bones* *in pyelonephritis* and *chronic otitis media* In rare circumstances it may produce primary disease including septicemia endocarditis or pyelitis as a *terminal event* in an individual debilitated by some severe or chronic disease

Pyocyaneus is resistant to penicillin but extremely sensitive to *streptomycin* which may be utilized parenterally in the treatment of wound or urinary infections (p 104)

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pertenue the etiological agent in frambesia (yaws) and *Tr carateum* the etiological agent of pinta

Borrelia—The 1. species of borrelia include six which are causative agents in *relapsing fever* *B vincentii* is associated with fusospirochetosis and *B refringens* is a harmless organism found around the genitals and important only in that it may be mistaken for *Tr pallidum*

Leptospira—Of the 4 species of leptospira only two are pathogenic for man the *L hebdomadis* is the etiological agent of Japanese seven day fever and the *L icterohaemorrhagiae* is the incitant of Weil s disease or infectious jaundice

Spirillum—The *spirillum minus* of rat bite fever is included with the spirochetes though the classification of the organism is still debatable For purposes of convenience it is considered in the present section together with its associated *Streptobacillus moniliformis*

GENERAL BIOLOGICAL CHARACTERISTICS

The spirochetes do not stain well with the usual bacterial dyes Methylene blue and the Gram stain are of little value Wright s and Giemsa as used for blood smears produce better results but of chief value is the darkfield microscopic examination of fresh wet smears (p 45) In tissue the silver impregnation method of Levaditi is useful but this has no practical value for routine use

Immunity Reactions—As antigens the spirochetes resemble bacteria they induce the production of agglutinin and precipitin and complement fixing and lytic antibodies Pathogenic spirochetes probably form endotoxins or "aggressins of the type described for bacteria they do not form exotoxins

Culture—Almost all spirochetes can be cultured in the test tube but the technics are difficult they are kept alive more readily in the tissues of suitable experimental animals

Responses to Therapy—Immunotherapy is of limited value in the spirochetal diseases but chemotherapy achieves brilliant results with arsenicals and penicillin

only on the Island of Malta in patients who drink the raw milk obtained from goats In the absence of any other explanation a possible brucellosis should be considered in patients with vague muscle and joint pains low grade febrile disturbances neurasthenics and in those with an unexplained splenomegaly arthropathy or spondylitis On very rare occasions the typical *undulation of the fever* is observed as in the Malta Fever variety If it is possible to eliminate the presence of tuberculosis malaria subacute bacterial endocarditis influenza chronic pansinusitis rheumatic fever and the blood dyscrasias a special battery of tests designed to establish a laboratory corroboration of the clinical condition is warranted

Laboratory Data —The laboratory aids in diagnosis include blood and tissue cultures an agglutination reaction a skin test with vaccine or brucellergin and the opsonophagocytic index

Isolation of the Brucella —The only certain diagnostic test for the presence of brucellosis is the isolation and identification of the organism *Bacteremia* is usually present only in the acute pha es of the disease or the acute febrile exacerbation of chronic disease as in *undulant fever*

Cultural work is limited by the difficulties of technic and the transitory nature of the bacteremia If primary direct isolation of the organism is not possible blood may be injected intraperitoneally and subcutaneously in guinea pigs The animals are kept alive for at least two months and skin tests and agglutination reactions are performed at intervals Should these become positive the animals are sacrificed and cultures of the organs are made The complexity of these procedures places them quite beyond the range of even the well equipped hospital but they may be performed by the experts of the United States Public Health Service

Agglutination —A rapid slide agglutination technic has been developed using the *patient s serum* and a *commercially available antigen* In general a titer of 1 40 to 1 80 should excite suspicion and call for further study On the other hand the test has many limitations Agglutinins are ordinarily not found until the second week of the acute illness the titer may be quite variable and some patients never develop demonstrable agglutinins in chronic brucellosis it is not uncommon to have a low titer or none at all and finally patients who have recovered from the disease may continue to exhibit a high titer of brucella agglutinins even though they are suffering from some other unrelated disease at the time the test is performed

With these considerations in mind it must be concluded that *the test has little positive value* but may be useful if there is demonstrable a rising titer during an otherwise obscure febrile illness

Skin Tests —The skin test is performed with *Huddleson s brucellergin* a nucleoprotein fraction of brucella of uniform composition and potency The antigen is injected intradermally in the forearm A *positive reaction* to 0 1 cc consists of erythema and induration from ½ to 3 inches in diameter reaching its height in forty eight hours A mild transient erythema without induration can be disregarded (see Fig 45 p 318)

The skin test indicates hypersensitivity to brucella or its neucleoprotein fraction and a *positive reaction* points to present or past brucella infection Since hypersensitivity persists for years after an active inflammatory process the positive skin test does not necessarily mean that the patient is suffering from the disease at the time that the test is done With rare

do not commonly develop neurosyphilis although it is unlikely that they are infected with *different strains of spirochetes than white persons* *It is more likely that the varied clinical* manifestations result from differences in natural and acquired immunity as best illustrated in the considerations of *yaws* (p 351) and *pinta* (p 353) grouped by some authorities with syphilis as *treponematoses*

Experimental Syphilis—Apes monkeys rabbits mice and guinea pigs can be infected with *Treponema pallidum* Experimental syphilis has been studied extensively in rabbits which when injected intratesticularly with tissue suspensions containing *Treponema pallidum* develop swelling of the testicles to the size of a pigeon s egg after an incubation period of two to six weeks A superficial ulcer or a typical chancre appears at the site of inoculation The testicular lesion may persist for months or for more than a year Metastatic lesions may develop in any organ and these include cutaneous eruptions as well as granulomatous and ulcerative lesions of the skin onychia and paronychia destructive lesions of periosteum and bones and various types of inflammation of the eye The dissemination of infection is apparent from the facts that lymph nodes and tissues generally become infective for other rabbits within forty-eight hours after scrotal inoculation and the blood becomes infective within a week Some of the rabbit strains have been kept alive for more than twenty years by animal passage and are still virulent

The differences in experimental syphilis in various animals lend support to the view that yaws and pinta are altered manifestations of syphilis occurring in hosts with changed tissue reactions

Epidemiology—Syphilis is widely prevalent throughout the world and presents a tremendous problem in the United States Each year it is estimated that there are between 500 000 and 600 000 new infections and more than 50 000 infants with congenital syphilis are born annually The domiciliary care of patients with general paresis is estimated at $31 000 000 annually with an additional $10 000 000 spent for the syphilitic blind Cardiovascular syphilis is reputedly the cause for 40 000 deaths each year and estimates of the overall incidence of Wassermann positivity in the United States approximate 10 per cent or in excess of 10 000 000 persons

Infectivity—Infectivity in syphilis is difficult of definition *Chancres secondary skin lesions* and particularly *mucous membrane manifestations* are highly infectious but the *blood* of a syphilitic is probably no longer infectious regardless of the serological reaction if he has had the disease more than five years *Late cutaneous lesions* (p 3? 6) should be regarded as infectious since spirochetes may still be present *congenital lesions* are highly dangerous

Genital Syphilis—Syphilis results from the direct transmission of *Treponema pallidum* from one person to another in more than 95 per cent of all instances Implantation is from one cutaneous or mucous surface to another by *sexual intercourse*

Extragenital Syphilis—Extragenital infection by kissing and accidental infection of the fingers accounts for a small percentage of cases Since the organism readily dies outside the tissues of the host and is especially sensitive to drying and moist heat instances of infection by indirect methods are very rare

Congenital Syphilis—Congenital syphilis is always the result of syphilis in the mother since there is no evidence that the sperm can infect the ovum and produce a syphilitic fetus without maternal involvement Probably there is a spirochetemia in the mother during the course of the pregnancy spirochetes localize in the maternal placenta and make their way through the villi and into the fetal circulation The mother of every syphilitic child is herself syphilitic although she need not necessarily infect the fetus

Transfusion Syphilis—Transfusion syphilis has become a recent problem Considering the vast numbers of transfusions administered the incidence of transfusion syphilis is small but it should not be permitted to occur at all Obviously more stringent rules are needed for the physical examination of donors *Primary infectious syphilis* exists in a seronegative stage and this may be overlooked if blood tests are done without physical examination Blood that has stood in the refrigerator for three or more days is probably safe since spirochetes quickly die at temperatures below 6 C

Immunity in Syphilis—The problem of immunity has important practical aspects in the diagnosis and treatment of syphilis

Natural Immunity—Natural immunity to syphilis does not exist among human beings although different animal species vary in their reactions to the disease Rabbits develop generalized lesions but mice and guinea pigs suffer inapparent infect[illegible] spirochetes

though it may be of some corroborative value in terms of the agglutination and skin reaction

PROGNOSIS

The statistical reports concerning brucellosis are unreliable since it is not known how great may be the frequency of the disease Only the dramatic and clearcut manifestations such as undulant fever or meningitis are recorded In these the case fatality approximates 2 per cent Of much greater gravity is the chronic invalidism produced by this disease if its incidence is as great as most investigators are prone to believe

TREATMENT

The control of brucellosis is essentially a *public health problem* Eradication of the disease in cattle has already been undertaken by state and

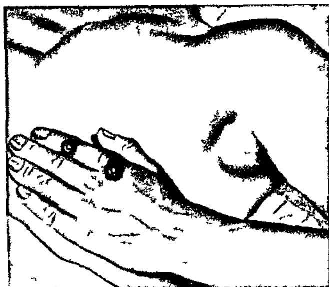


Fig 4 —Primary lesion of tularemia Note the elevated periphery of the ulcers and also the characteristic axillary lymphadenopathy

federal agencies and much progress is already reported The universal *pasteurization of milk* is the simplest and most effective measure for the elimination of the bovine form of the disease in man However even when this objective has been obtained the problem of porcine brucellosis remains since in some areas of the United States this form of the disease is more prevalent than the bovine variety

Symptomatic Treatment —During the period that specific therapy is being attempted the general management of the patient involves bed rest and the same principles involved in caring for the person who has typhoid fever (p 236)

Anti Brucella Serum —An *anti brucella serum* has been prepared by Foshay and appears to be of some value in the acute phases especially

Sharp and Dohme Sem May 1944

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advantage over the Foshay preparation in that sensitivity to horse serum need not be considered

Vaccine—Vaccine therapy has given way to *injection of brucellergin* as prepared by Huddleson The preparation is given in sufficient doses to cause four or more sharp febrile reactions Those who advocate its use say that 60 per cent of the patients achieve a complete recovery Critics of the method are inclined to believe that the benefits are due to a non specific protein reaction and favor the substitution of the intravenous injection of typhoid vaccine or the intramuscular injection of boiled milk

Hyperthermia—Because of the improvement following the febrile reactions produced by biological agents artificial fever therapy has been attempted and is occasionally effective

Anti infective Therapy—There is no great promise from anti infective therapy in the problem of the treatment of brucellosis The organism is not sensitive to *penicillin* and *sulfonamides* are administered only in a proba tory fashion Those who believe that brucellosis is essentially an enteric fever favor the administration of an insoluble sulfonamide such as *sulfa guanidine sulfasuxidine* or *sulfathalidine* others impressed by the diffuse systemic manifestations utilize a soluble sulfonamide such as *sulfadiazine*

It would be our opinion that trials with soluble and then insoluble sulfonamides are justified in both the acute and chronic forms of brucel losis Streptomycin therapy despite early encouraging reports appears to be ineffective in both the acute and chronic forms of the disease However it merits probatory or desperation trial (p 114)

Because of the variable character of the disease it will be many years before a definitive evaluation of specific anti infective therapy can be reached Until that time the practitioner is justified in being a therapeutist first and a scientist later

PLAGUE

Plague an infectious disease of rats caused by the *Pasteurella pestis* may be transmitted from *rat to man* and from *man to man* In times past it has been one of the great epidemic scourges of Europe and Asia and it is still endemic in many parts of the world especially at seaports where infected rats escape from a ship in port At the present time there is an endemic focus of plague among *ground squirrels* and other *wild rodents* in California and other western states with recent local epidemics of human plague in Los Angeles and San Francisco (sylvatic plague)

Bacteriology and Immunology—*Pasteurella pestis* is a small ovoid bacillus characterized by a bipolar staining reaction It produces *endotoxins* but no exotoxin and is *highly invasive* usually causing *septicemia*

There appears to be little or no natural immunity to plague although recovery from an attack of the disease is accompanied by the development of agglutinins opsonins and bacteriolysins These usually appear too late to be useful as clinical tests and the laboratory diagnosis is made by smears or cultures of buboes blood or sputum

Transmission—Plague is maintained among rats by the *rat flea* an insect vector A human epidemic is usually preceded by a *rat epizootic* and when rats and men live in close association rat fleas deposit infective material on the human skin producing the bubonic type of the disease During the height of an epidemic the pneumonic type may occur and this variety is spread directly from man to man by droplets of sputum without requiring the intermediary participation of the flea

of the patients whose spinal fluids are examined during the infectious sta e of the disease already shows manifestations of invasion

IMMUNITY IN RELATION TO TREATMENT—If it is true that the mechanisms of tissue immunity are stimulated by the spirochete s presence in the chancre and later in the secondary lesions of the skin and mucous membranes the argument to defer treatment is not without reason It was with this thought in mind that the patients reported by Bruusgaard were deprived of treatment at any time Similar reasoning led to the delay of treatment in former days until the secondary eruption had appeared and many present authorities utilize this same process of argumentation in opposing prophylactic chemotherapy in those who are known to have been exposed to syphilis and in condemnation of the recently introduced methods of intensive arsenotherapy These theoretical considerations find some justification in the observation that incompletely treated syphilis often runs a more malignant course than neglected syphilis

Despite our profound realization of the importance of tissue immunity we favor the *earliest and most intense attack on the organism* in the management of infectious syphilis We treat those who are known to have been exposed to syphilis *before* they have developed the primary lesion and if we should ever ourselves become infected *we should submit to one of the newer forms of intensive treatment at the earliest possible moment*

Allergy and Syphilis—Allergy or hypersensitiveness may be as important in syphilis as it is in tuberculosis The *gumma* which is a relatively rapid necrosis of tissue in the presence of very few spirochetes is suggestively similar to an allergic reaction The allergic state in syphilis is said to result in an increased tendency for the skin to react excessively to the injection of nonspecific substances In view of a possible allergic state in syphilis many attempts have been made to devise diagnostic skin tests The *luetin* of Noguchi which was composed of killed suspensions of *Treponema pallidum* was extensively studied While positive intradermal reactions with this and other test antigens have been obtained the results are too inconclusive and variable to have any usefulness as diagnostic tests

The Diagnostic Tests—There remains for discussion the nature of the substance present in the blood and spinal fluid of syphilitics which accounts for the *complement fixation* of Wassermann and for the *flocculation tests* (p 337) of Kahn Kline Hinton Ea le and others Wassermann s original antigen consisted of tissue containing spirochetes and he naturally assumed that the antigens of the spirochete were specifically concerned in the reaction But it was soon found that normal tissues served equally well as antigens for the test At the pr sent time normal beef heart muscle is the material most widely used as the source of the Wassermann antigen The alcoholic extracts of beef heart muscle contain various lipoids which react with the substance present in syphilitic serum The addition of cholesterol greatly enhances the sensitivity of the lipoids to flocculation or to complement fixation but there is as yet no agreement as to the nature of the substance that causes the serological reactions Whether it is a true antibody produced in response to the antigenic stimulus of *Treponema pallidum and reacting with nonspecific lipoids because of chemical similarities* is not known It may be noted that whatever the nature of the substance it is the same for the complement fixation and the flocculation tests When one test is positive and the others negative as sometimes happens the discrepancy is probably the result of a technical error

Whatever its nature the Wassermann antibody or *reagin* is also present in leprosy malaria relapsing fever yaws pinta infectious mononucleosis and rat bite fever Until we learn more of the composition of the substance it is idle to speculate on the reasons for its presence in this diverse array of diseases

Pathology—There is nothing pathognomonic about the histological changes in syphilis The most typical feature of the pathological process is the perivascular collection of lymphocytes and plasma cells The early lesions do not destroy tissue but the later lesions may produce necrosis Early lesions swarm with spirochetes while late lesions have relatively few

The *gumma* is a necrotic localized syphilitic lesion which develops in the late stages of the disease The inflammatory tissue is chiefly composed of lymphocytes and plasma cells The blood vessels show *periarterial inflammation and endarteritis In the center of the lesion* necrosis and caseation occur with the formation of a peculiar gummy material At the margins of the necrotic area giant cells may be seen but they are not as common as in tuberculosis Fibroblastic proliferation takes place around the lesion

TULAREMIA (DEER FLY FEVER)

Tularemia derives its name from Tulare County California where the disease was first described It is essentially a disease of rabbits ground squirrels mice rats deer skunk beaver and other wild animals The infection is transmitted from animal to animal by flies and ticks *Man is accidentally infected by the bite of an infected tick or deer fly and by handling sick animals*

Bacteriology —The causative agent is a small pleomorphic gram negative nonmotile nonspore forming aerobic bacillus related to the Pasteurella and Brucella It is rather fastidious in its nutritional requirements and grows best on a blood glucose-cystine agar The organism is highly invasive and is able to penetrate the unbroken skin The pathological lesion in lymph nodes and at the site of inoculation consists of a tubercle-like lesion with central necrosis epithelioid cells and fibroblastic proliferation at the periphery Septicemia is common

Epidemiology —Tularemia has been reported in almost every state in the United States as well as in Russia Japan and many of the countries of northern and western Europe It is most prevalent in the *western and central* states of this country The most common method of infection is the *handling of sick wild rabbits or squirrels* It is said that 1 per cent of wild rabbits are infected and the disease is seen among hunters butchers and others who skin and dress these animals Infection has also resulted from eating infected rabbit that was improperly cooked Laboratory workers farmers and cattlemen are in considerable danger of contracting the disease

Immunity —As immunity to tularemia develops *agglutinins* and *opsonins* appear in the patient's blood *Agglutinins* are absent during the first week of the disease but begin to rise during the second week and reach their maximum titer at about the fourth week They may persist for many years The development of *allergic sensitivity* to the organism precedes the appearance of agglutinins since a positive skin reaction to killed *tularense organisms* can be noted as early as two or three days after the onset of symptoms

CLINICAL MANIFESTATIONS

The *incubation period* of tularemia is usually three days but may vary from one day to three weeks The clinical symptoms begin acutely with headache prostration malaise chilliness or frank chills and temperatures up to 104° F Later the disease manifests itself as an ulceroglandular oculoglandular glandular or typhoidal variety

Ulceroglandular Type —The ulceroglandular variety of the disease occurs in 85 per cent of all cases Soon after the onset of systemic symptoms the skin overlying the regional lymph nodes that drain the site of inoculation becomes red tender and painful These lymph nodes may remain hard and tender for two or three months and then slowly resolve or they may soften suppurate and rupture through the skin

Within a day or two after the lymphadenitis develops a painful inflamed *papule* appears on the skin at the site of penetration of the organisms and streaks of *lymphangitis* extend from this primary lesion toward the regional lymph nodes The primary papule later becomes necrotic and disappears leaving a dry black punched-out *ulcer* about a centimeter in diameter At times *subcutaneous nodules* resembling sporotrichosis appear in crops along the course of the lymphatics between the ulcer and the regional lymph nodes They are firm tender and movable but may break down and discharge pus for many weeks See Fig 47 p 319

Oculoglandular Type —The oculoglandular type of tularemia is essentially similar to the ulceroglandular type except that the primary lesion

Diagnosis

The diagnostic survey in syphilis has a dual purpose The first objective is the establishment of the presence of the disease the second is the determination of the extent of tissue damage that has occurred

TABLE 22—CLINICAL MANIFESTATIONS OF SYPHILIS

Primary Seronegative

Chancre (p 331) with positive darkfield and negative serology

Primary Seropositive

Chancre (p 331) with positive darkfield and positive serology

Secondary

Mucocutaneous lesions (p 338) and constitutional symptoms positive darkfield and serology

Infectious Syphilis

Ordinarily used to signify primary secondary prenatal and pregnancy syphilis it may also include tertiary lues in which spirochetes are demonstrable in the gumma

Early Latent

Asymptomatic with positive serology within 5 years of infection negative spinal fluid

Late Latent

Asymptomatic with positive serology later than 5 years after infection negative spinal fluid

Asymptomatic Neurosyphilis

Latent syphilis with positive spinal fluid blood may be negative

Tertiary Syphilis

Gummas anywhere but usually cutaneous osseous (p 2938) hepatic (p 1963) or testicular (p 2465) blood may be negative but therapeutic test with iodide is confirmatory

Neurosyphilis (p 1465)

Asymptomatic tabes dorsalis general paresis meningovascular meningitic gummatous cranial nerve paralysis ocular (p 1605) auditory (p 2019) spinal fluid positive but blood may be negative

Cardiovascular (p 1095)

Aortitis endarteritis myocarditis blood may be negative

Visceral

Pulmonary (p 2787) gastric (p 1766) laryngeal (p 2161) hepatic (p 1963) osseous (p 2938) arthritic (p 2939) testicular (p 2465) blood may be negative

Prenatal

Syphiloderms dactylitis periostitis osteomyelitis snuffles keratitis Hutchinson teeth blood positive lesions darkfield positive

Pregnancy

Miscarriages stillbirth

Darkfield Examination—The definitive diagnosis of infectious syphilis is established only by the demonstration of the organism by *darkfield microscopy* In primary syphilis when infectivity is at its height and the importance of immediate treatment is greatest the recognition of the nature of

tion tests for tularemia are performed such patients may be mistakenly diagnosed as having tuberculous pleurisy with effusion

Meningitis is a rare complication of tularemia and is secondary to septicemia It is almost always fatal

PROGNOSIS

The overall case fatality rate of recognized tularemia is only 4 per cent In terms of prolonged disability tularemia is a serious disease The pneumonic forms of the disease have a mortality rate of 30 per cent while the uncommon typhoidal type may have a fatality rate of 50 per cent In the presence of meningitis the prognosis is ominous

DIAGNOSIS

The diagnosis of tularemia is suspected when there is a history of contact with wild rabbits or a tick bite in an area in which this disease is endemic

Laboratory corroboration of the clinical diagnosis requires expert assistance such as is provided by the United States Public Health Service *Blood cultures* are required to be taken with the utmost care since laboratory infections are frequent and the growth and identification of the tularense require considerable experience and equipment The organism also may be isolated from guinea pigs inoculated with blood or material aspirated from the involved nodes

Less definitive information is obtained by the observation of a skin reaction using killed organisms and by the agglutination titer The *skin reaction* as in other diseases merely means a hypersensitivity to the protein of the bacterium It should not be interpreted as indicative of active disease but may be merely a residuum of a previous infection The interpretation of *agglutinin titers* is confusing in that cross agglutination occurs with *brucella abortus* The serological data are of significance if a higher titer is demonstrable later in the course of the disease

On clinical grounds alone it is impossible to differentiate the primary lesion from that of *syphilis lymphopathia venereum* or *sporotrichosis* It is essential to do a darkfield examination for spirochetes (p 45) a Frei test (p 473) in lymphopathia venereum and a search for the characteristic organism in sporotrichosis

TREATMENT

An *antitularemia serum* has been produced by Foshay in horses and goats An average dose of 30 cc is administered intramuscularly or intravenously early in the course of the illness if it is at all possible A double dose is required if pulmonary complications are present and the initial dose may be repeated in two or three days if there is no clinical evidence of improvement Those who advocate the use of serum maintain that it is effective in shortening the course of the disease in preventing complication and in reducing mortality Serum sickness of considerable severity may be expected The use of blood and serum of convalescents has also been favorably reported

Overzealous *surgical treatment* of the involved lymph nodes should be avoided lest the infection be disseminated If the glands suppurate a small

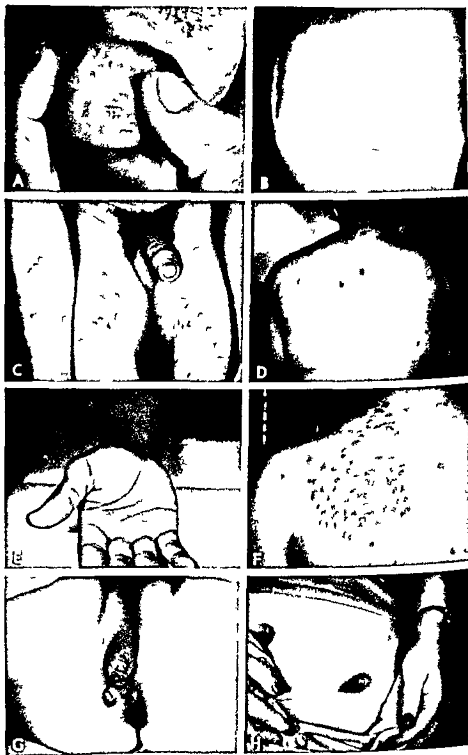


Fig 49 —Clinical manifestations of syphilis Secondary and tertiary syphilis *A* Mucous patch of lower lip *B* Macular syphilid of body *C* Varioliform syphilid of legs *D* Erythema multiforme-like syphilid of back *E* Papular syphilid of palms *F* Maculopapular syphilid at site of mustard plaster *G* Gumma of vulva *H* Gumma of thigh

CHAPTER 11

BACILLARY INFECTIONS MISCELLANEOUS

Glanders (*Malleomyces mallei*)
B mucosus capsulatus (*Klebsiella pneumoniae of Friedlander*)
Erysipeloid (*Erysipelothrix rhusiopathiae*)
Pyocyaneus (*Pseudomonas aeruginosa*)

GLANDERS (FARCY)

GLANDERS a disease of horses and mules may be transmitted to n by direct contact with infected animals It is likely to occur in stablem grooms and others who are in close contact with horses The causat agent is the Bacillus mallei a small cocco bacillus which grows reac on most laboratory media and does not produce soluble exotoxins

CLINICAL MANIFESTATIONS

Human glanders may assume an acute or chronic form The *acute* fc becomes manifest by fever and systemic symptoms following a brief incu tion period of several days The characteristic lesions are *nodules* wh later become abscessed They may be observed in the skin the nose larynx and bronchi in muscles and tendons or in the periosteum of bor Arthritic symptoms and pneumonitis may occur

In the *chronic* form of the disease the abscesses are more indolent a may drain for long periods Healing of one lesion is commonly follow by formation of others The prognosis of the acute disease is grave I in the chronic stage the outlook is somewhat better

DIAGNOSIS

A history of contact with horses and the presence of an infectious dise characterized by skin and visceral abscesses should lead to the suspici of glanders The bacteriological diagnosis is made by recovering the orga ism from the abscesses of the skin or mucous membranes When pus cc taining *Bacillus mallei* is injected intraperitoneally into a male guinea p swelling and necrosis of the testicles develop in twenty four to thirty hours and the organisms can be recovered from these lesions

A skin test with an extract of the bacillu (*mallein*) is of some di nostic value

TREATMENT

There are as yet no reports of the effects of the anti infective ager in the treatment of glanders Until such time as these are definitely prov to be useless the practitioner is justified in prescribing *sulfonamide penic lin* or both agencies in order that he may observe for himself the clini results The favorable results of sulfonamides in melioido is an allied fection augurs well for specific therapy

Course

The unmodified course of syphilis is best comprehended by a consideration of the remarkable studies of Bruusgaard who attempted to learn the fate of 2181 untreated patients afflicted with primary or secondary syphilis He was able to obtain information concerning 473 or 22 per cent Of this small group 309 were alive and only 35 per cent had clinical evidences of syphilis Of the 164 who had died only 30 per cent had died of syphilis From these findings, it seemed fair to suggest that the patient infected by the spirochete has approximately one chance in three of actually suffering from or dying of his disease

The Bruusgaard series showed that 22 per cent of the living had positive serologic findings but no clinical evidences of their disease Most remarkable of all 43 per cent of the patients followed were clinically well and serologically negative and had apparently enjoyed a spontaneous cure The total of spontaneous cures and asymptomatic latency with positive serology thus reached the figure of 65 per cent or approximately two thirds of those who had been originally infected

If the Bruusgaard figures do nothing else they may be utilized to reassure the patient that he will not necessarily die of syphilitic heart disease or insanity as many lay writers would have him believe They serve also to caution the therapist against overzealousness in his chemotherapeutic approach during the period of late latency

Treatment

Despite a bewildering variety of treatment methods for syphilis four basic plans present themselves for use by the practitioner There is the choice of *penicillin intensive arsenotherapy ambulatory conservative treatment* as outlined by the Cooperative Clinical Group and a form of *intensified ambulatory treatment* as recommended by the United States Army

Penicillin

Despite its recent introduction there is already little doubt as to the efficacy of penicillin in the treatment of primary and secondary syphilis From available evidence it is clear that a total dose of 1 200 000 units suffices for most early primary infections but some of the older and more resistant secondary invasions call for a total of 2 400 000 units Our preference is for the larger dosage since it is our belief that in view of the negligible toxicity of the remedy the practitioner should err on the side of excessive amount and employ at least 10 million units

Technic —The recommended technic requires *intramuscular injections* at three hour intervals To deliver 2 400 000 units 60 consecutive injections are given each of 40 000 units The completion of this schedule requires somewhat less than eight days

In private practice it is our opinion that a total of 10 million units should be employed Individual doses of 100 000 units are injected intramuscularly at 3 hour intervals night and day for twelve days Considering the lack of toxicity of the antibiotic (p 106) and the menace of the infection it is well to apply the principle of extravagant overdosage rather than wait for statistics to justify the use of lesser amounts

CHAPTER 12

SPIROCHETAL INFECTION GENERAL CONSIDERATIONS

The spirochetes are unicellular organisms which appear to be more closely related to bacteria than to protozoa They are widely distributed in nature The majority are saprophytic and free living while a few are parasitic including *Treponema pallidum* the cause of *syphilis*

Spirochetes have a simple structure similar to bacteria They are motile but do not possess flagella Instead they move by flexion of the coiled body and by rotation about the long axis They reproduce by transverse fission Almost nothing is known of their metabolic activities Their resistance to physical agents and chemical disinfectants is in general less than that of the vegetative forms of bacteria

KEY TO THE GENERA OF FAMILY SPIROCHAETACEAE

A Cell 4› to 500 microns long forming a helix with large irregular or inconstant coil Altered but not disintegrated by 10 per cent bile salts

1 No crista or ridge

a Protoplast wound spirally around a well-defined axis filament No obvious periplast membrane and no loculation Fresh water and marine forms especially in the presence of H S Genus I *Spirochaeta*

b No evident axis filament Distinct periplast membrane Found in *Foraminifera* ooze Genus II *Saprospira*

2 Crista or ridge present Periplast membrane demonstrable Axis filament and loculation seen when stained Parasite in Mollusks Genus III *Cristispira*

B Cell 4 to 1 microns (rarely up to 40 microns in Leptospira) Commonly disintegrated by 10 per cent bile salts

1 Open irregular coils stain readily with aniline dyes other than the Giemsa stain Parasitic, many pathogenic some transmitted by arthropods Active lashing movements and slow rotation Genus IV *Borrelia*

2 Close permanent coils difficult to stain with aniline dyes other than the Giemsa stain

a Pitch of coil about 1 micron or slightly more Movements show bending and rotation Disintegrated by 10 per cent saponin Parasitic and many pathogenic to mammals Genus V *Treponema*

b Pitch of coils about 0 5 micron or slightly less Movements rapid spinning and intermittently active lashing One or both ends recurved Resistant to 10 per cent saponin Some parasitic and pathogenic to mammals others found in water Genus VI *Leptospira*

Spirochaeta, Saprospira and Cristispira —These genera of the spirochete family are made up of large saprophytes which have no medical significance

Treponema —The treponemas are parasitic and frequently pathogenic forms with undulating or rigid spiralliform bodies They are without crista or columella they may or may not have flagelliform tapering ends Six of the eight species of treponemas recognized u the Bergey's Manual are of no medical significance except in that they may be confused with the pathogens The latter pathogens include *T pallidum* the cause of syphilis *T*

1 Simmons J S and Gentzkow C J Laboratory Methods of the United States Army ed 5 Philadelphia Lea and Febiger 1944

its acceptance by the practitioner is the brevity of present observations and the lurking fear that long range results may not equal those of shorter term observations For ourselves despite our own participation in the introduction and conduct of intensive arsenotherapy by the method of the intravenous drip (Five Day Treatment) we are quite persuaded that penicillin is the drug of choice in syphilotherapy Were we ourselves afflicted, we should definitely want to be treated by penicillin since it holds so great promise for benefit and so little hazard We would be willing to supplement the antibiotic agency with intramuscular injections of *bismuth* but we should reserve arsenotherapy and hyperthermy for those instances in which there is penicillin failure

INTENSIVE ARSENOTHERAPY BY THE INTRAVENOUS DRIP METHOD (FIVE DAY TREATMENT)

Intensive arsenotherapy by the intravenous drip method requires hospitalization

Technic —The patient is put to bed and is given an intravenous drip of 2000 cc of 5 per cent dextrose in saline To the diluent are added the contents of 4 mapharsen ampoules of 60 mg (1 grain) each totalling 240 mg (4 grains) *The speed of the drip is regulated so that not more than 3 or 4 cc are delivered per minute* (60 to 90 drops) At this rate the total infusion is completed in 5 to 10 hours so that the treatment that is started early in the morning after the patient has breakfasted should be concluded in the late afternoon or early evening before dinner

The drip is repeated on each of five consecutive days No other injections are made at this time or later unless there is a treatment failure (p 347) under which circumstance the whole procedure is repeated

Toxicity —Massive dose arsenotherapy produces definite toxic symptoms On the first day there is usually considerable *nausea* and *vomiting* Toward afternoon there occurs a primary rise of temperature (*Herxheimer fever*) which may reach 103° to 105° F The drip is discontinued as soon as this phenomenon is noted but nothing is done to lower the temperature since the pyrexia is by way of being an adjuvant to therapy as better illustrated in fever treatment

Under ordinary circumstances the Herxheimer reaction is terminated in a few hours the patient suffers no ill consequences and can resume therapy in the morning The course of the next few days is relatively uneventful though nausea and vomiting may persist Toward the termination of treatment difficulties arise anew and there may be a second febrile rise this time of a gentler and a less tempestuous nature This *secondary fever* is usually accompanied by a *toxicoderm* which may be morbilliform scarlatiniform or urticarial The secondary fevers and toxicoderms are experienced in 10 to 15 per cent of those who begin treatment They have only nuisance value and thus are to be differentiated from the malignant dermatitis exfoliativa

During the course of intensive treatment the urine is carefully watched for evidences of *albuminuria* or *hematuria* and *surprisingly enough* these have not been encountered to any significant degree The patient urine and blood specimens are scrutinized for evidences of hepatic damage as manifested by *jaundice bilirubinuria* or *hyperbilirubinemia* again for

CHAPTER 12

SPIROCHETAL INFECTION GENERAL CONSIDERATIONS

The spirochetes are unicellular organisms which appear to be more closely related to bacteria than to protozoa They are widely distributed in nature The majority are saprophytic and free living while a few are parasitic including *Treponema pallidum* the cause of *syphilis*

Spirochetes have a simple structure similar to bacteria They are motile but do not possess flagella Instead they move by flexion of the coiled body and by rotation about the long axis They reproduce by transverse fission Almost nothing is known of their metabolic activities Their resistance to physical agents and chemical disinfectants is in general less than that of the vegetative forms of bacteria

KEY TO THE GENERA OF FAMILY SPIROCHAETACEAE

A Cells 4 to 500 microns long forming a helix with large irregular or inconstant coil Altered but not disintegrated by 10 per cent bile salts

1 No crista or ridge

a Protoplast wound spirally around a well-defined axis filament No obvious periplast membrane and no loculation Fresh water and marine forms especially in the presence of H_2S Genus I *Spirochaeta*

b No evident axis filament Distinct periplast membrane Found in *Foraminifera* ooze Genus II *Saprospira*

2 Crista or ridge present Periplast membrane demonstrable Axis filament and loculation seen when stained Parasite in Mollusks Genus III *Cristispira*

B Cells 4 to 16 microns (rarely up to 40 microns in Leptospira) Commonly disintegrated by 10 per cent bile salts

1 Open irregular coils stain readily with aniline dyes other than the Giemsa stain Parasitic many pathogenic some transmitted by arthropods Active lashing movements and slow rotation Genus IV *Borrelia*

2 Close permanent coils difficult to stain with aniline dyes other than the Giemsa stain

a Pitch of coils about 1 micron or slightly more Movements slow bending and rotation Disintegrated by 10 per cent saponin Parasitic and many pathogenic to mammals Genus V *Treponema*

b Pitch of coils about 0.5 micron or slightly less Movements rapid spinning and intermittently active lashing One or both ends recurved Resistant to 10 per cent saponin Some parasitic and pathogenic to mammals others found in water Genus VI *Leptospira*

Spirochaeta Saprospira and Cristispira.—The above genera of the spirochete family are made up of large saprophytes which have no medical significance

Treponema.—The treponemas are parasitic and frequently pathogenic forms with undulating or rigid spirilliform bodies They are without crista or columella they may or may not have flagelliform tapering ends Six of the eight species of treponemas recognized in the Bergey's Manual are of no medical significance except in that they may be confused with the pathogen The latter pathogens include *Tr pallidum* the cause of syphilis *Tr*

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95 per cent Against this accomplishment is the treatment mortality rate of 0.25 per cent or one patient in each 400 treated

Intensive arsenotherapy has the advantage that the patient is hospitalized during the florid and infectious phase of the disease treatment is completed in almost every instance the patient may be assured of "cure" in better than nine instances out of ten and those who are not cured have at most positive serology Neither visceral nor neurological syphilis has been encountered even in the unsatisfactory group

The addition of *bismuth* somewhat raises the incidence of favorable results Its persistent use after the patient has completed the hospital form of therapy may prevent infectious relapses and serologic reversal A disadvantage of intensive arsenotherapy is its toxic effects toxic encephalopathy constitute a challenge and a threat which thus far can be neither prevented nor anticipated although perfected products which are soon to be released by the United States Public Health Service hold promise for the detoxification of arsenical reactions

OTHER METHODS OF INTENSIVE TREATMENT

The introduction of the five-day treatment has given rise to experimental methods designed to bridge the gap between intensive therapy with its 0.25 per cent treatment mortality and conservative ambulatory treatment which claims but does not prove a lower risk

The variants include

1 *Multiple injection technic* whereby the patient is given two or three daily intravenous injections by the syringe method for five to eight days This method is cumbersome and apparently not wholly satisfactory since its most ardent advocates advocate simultaneous *fever therapy* alternating intravenous injections of *typhoid vaccine* with the arsenotherapy
2 *Hyperpyrexia* which has a solid experimental foundation for use in infectious syphilis Patients must be institutionalized and observed with great care in specially equipped hospitals In general, a fever of 106 F or more is accomplished and sustained for five to eight hours Mapharsen 60 to 120 mg is injected intravenously during the febrile period and this constitutes so-called *"one-day treatment"* This technic is quite beyond the scope of the practitioner It seems not without toxicity since an appreciable number of the treated developed a serious *azotemia*
3 *Combined methods* which employ *hyperpyrexia* and *multiple injection* Advocates of chemotherapy rely mostly on injections and use fever as an adjuvant whereas one-day treatment is essentially a therapeutic hyperpyrexia with adjuvant chemotherapy
4 *Shortened conservative treatment* which utilizes the total dosage of the five-day method, approximating 1200 mg Multiple injections are given three times weekly for six eight and ten weeks attempting to obtain similar results with lesser toxicity Weekly injections of bismuth are included This technic could be used by the practitioner if the expectations are confirmed by the tabulated results relative to toxicity and curability

AMBULATORY CONSERVATIVE TREATMENT (COOPERATIVE CLINICAL GROUP)

The treatment schedule that is recommended by the Cooperative Clinical Group for the ambulatory management of early syphilis calls for the injection of *seventy doses of mapharsen and thirty two of bismuth* The span of time that is occupied in the completion of this routine is approximately sixty seven weeks or almost a year and a half

Arsenotherapy.—The schedule is initiated by a course of twenty intra

CHAPTER 13

SPIROCHETAL INFECTIONS TREPONEMA

Syphilis (*Treponema pallidum*)
Frambesia (*T eponema pertenue*)
Pinta (*Treponema carateum*)

SYPHILIS

Syphilis is an infectious disease caused by the *Treponema pallidum* Infection may be acquired or congenital The latter is in reality an invasion acquired in utero The disease is characterized by a primary or initial sore (*chancre*) followed by the development of *secondary lesions* of the skin and mucous membranes After a variable period of latency *tertiary visceral involvement* becomes manifest by a bewildering variety of lesions The *quaternary afflictions* of the nervous system include general paresis and tabes dorsalis (locomotor ataxia)

Etiology—The *spirochete of syphilis* is 4 to 15 µ in length with 8 to 20 *regular* tightly wound spirals It is actively motile as seen in *darkfield preparations* (p 4) It does not stain with the usual aniline dyes but can be demonstrated in wet preparations by India ink staining and in tissues by Levaditi's silver impregnation method In material from fresh lesions or cultures the preferable method of examination is by darkfield technic

The organism is more sensitive to heat than the vegetative forms of most bacteria Rabbit strains can be killed in vitro in one hour at 41.5 C in two hours at 41 C in three hours at 40 C and in five hours at 39 C This sensitivity to heat may explain the efficacy of *fever therapy* (p 359) in neurosyphilis The spirochete is also destroyed rapidly by drying and by ordinary antiseptics At 0 to 6 C it dies in one or two days so that plasma or blood from a syphilitic subject stored in the *refrigerator for several days* is noninfectious

Cultures—Noguchi in 1911 was the first to culture the *Treponema pallidum* using a medium of diluted serum containing a piece of sterile rabbit kidney or testes The *medium* was seeded with syphilitic rabbit testes sealed with paraffin and incubated at 37 C Growth occurred in ten or twelve days and by further transfers pure cultures were obtained which remained virulent for rabbits Noguchi succeeded also in cultivating the organism directly from human lesion After several transfers the spirochetes were capable of *producing chancres in monkeys* but later the cultures became avirulent The organism has also been cultivated on the *surface of blood* agar plates using anaerobic methods

In contrast to these positive claims reputable and *competent workers* have repeatedly failed to cultivate *Treponema pallidum* by any of the methods *employed* The *opinion* has been expressed that the organisms cultivated were actually saprophytic *spirochetes morphologically* resembling *Treponema pallidum* These discrepancies indicate that the growth requirements of the organism in vitro are poorly understood

The usual method of maintaining the Treponema is to inject mice or rabbits with it The organisms disseminate in the tissues and remain viable for an indefinite period When the strain is required for use a lymph node is excised from the infected animal ground up in a sterile mortar and injected into another animal

Strains—The protean nature of human syphilitic lesions leads to the hypothesis that there exist several strains of the organism The *dermatotropic variety* was thought to produce chiefly the cutaneous lesions while the *neurotropic strain* was believed responsible for tabes and paresis To substantiate this it was stated that the *occurrence of neurosyphilis* was *inversely* related to the severity of the earlier cutaneous lesions and that the *incidence* of neurosyphilis among conjugal partners was more than twice as great as in an unselected group of syphilitics Against the validity of the concept of strains is the fact that Negroes

vacation *another series of eight injections* is given at weekly intervals and, finally at the conclusion of the seventieth mapharsen injection, the treatment is terminated with *ten more weekly injections of the bismuth*

The total of the bismuth injections is therefore 32 and the intravenous and intramuscular administrations add up to 102 if mapharsen is employed.

When this treatment schedule has been completed the patient is not discharged but continues under observation In a certain percentage of individuals whose course is unsatisfactory the therapeutic endeavor must be repeated

Toxicity—The toxicity of ambulatory treatment cannot be estimated with accuracy Of patients who institute this prolonged and burdensome method of therapy 84 to 95 per cent lapse from treatment many undoubtedly for the very reason that they have suffered untoward symptoms. These reactors in consequence fall into the lost group and the available statistics naturally deal with the persons whose course has been followed Whatever may be the incidence of treatment morbidity and mortality the types of disturbance encountered in arsenotherapy (p 122) include minor symptoms such as *nitritoid crises nausea vomiting salivation headache chills fever* and *paresthesias* as well as the major syndromes of *toxic hepatitis thrombocytopenic purpura nephropathies dermatitis exfoliativa toxic encephalopathy peripheral neuritis* and *aplastic anemia*

Results—The results of ambulatory treatment of early syphilis are difficult of evaluation because of the enormous case loss Results in large well-established clinics show that if those who fail to complete therapy are considered as unfavorable the satisfactory issues do not exceed 16 per cent If the case loss is forgotten however and the recalcitrants are omitted from calculations the best available figures indicate that 66 7 per cent are clinically and serologically clear 15 per cent are clinically well but give positive serologic results (STS) 12 per cent develop neurosyphilis and — per cent have other manifestations of infection (Padgett) The results in late latent visceral and neurological syphilis are even less impressive especially if the Bruusgaard experience (p 340) is used as a yard tick

ACCELERATED AMBULATORY TREATMENT OF SYPHILIS ACCORDING TO THE SCHEDULE OF THE UNITED STATES ARMY

With the introduction of intensive arsenotherapy by the method of the intravenous drip it became apparent that the schedule recommended by the Cooperative Clinical Group with its excessive case loss necessitated acceleration A highly satisfactory compromise has been employed by the United States Army which uses injections of mapharsen and bismuth for a period of only twenty six weeks

Technic—During the course of the first five weeks the patient receives two weekly injections of mapharsen and one of bismuth from the sixth to the tenth weeks the two weekly injection of mapharsen are continued and after this time there is a mapharsen holiday" until the seventeenth week During the arsenic holiday weekly bismuth injections are given to the number of six The bismuth is then discontinued and on the seventeenth week another course of two weekly mapharsen injections is initiated for ten weeks which brings the patient to the half year mark From the twenty second to the twenty sixth week the mapharsen injections are up-

invade their tissues and rema n there indefinitely in a latent state Among humans different races exhibit certain differences in the types of syphilitic lesion they develop Negroes escape neurosyphilis but develop cardio ascular disease *Yaws* and *pinta* may be altered manifestations of syph lis due to changes in host reactions

It is evid nt that some type of alteration in host parasite relationship has occurred during the past four hundred years Syphilis was an epidemic disease of great virulence in the sixteenth century Florid secondary lesions were common and death often occurred at this stage of the disease To lay host and paras te appear to have reached a balance which permits them to live togeth er for long periods of time almost in symbiosis The result i a d sease of *great ch onicity* and *slow progression* This may be due to decreased virulence on the part of the pirochete but is more likely due to an alteration in natural resistanc on the part of the host

Acquired Immunity—Immun ty to syphilis is acquired as a result of infection The nature of this phenomenon is obscure but it is presumably a tissue immunity which depends in large part on the cont nued presence of spirochetes in the organs of the host Despite many efforts *humoral ant bodies* such as agglutinins and spirocheticidal substances cannot be demonstrated in the blood of syphilitics

Not all of the tissues of the body share equally in the immunity reaction In the early stages of the disease the spiroch tes presumably invade all of the tissues of the body yet certain organs are more likely than others to develop clinical lesions The frequency of syph lis of the skin and nervous system and the rarity of involvement of the stomach suggest that there are poss ble local variations in immun ty although special metabolic and environmental characteristics of these organs may explain the specific predilection of the spirochete for one tissue in preference to another

Sex apparently influences immunity since women more commonly than men reach a stage of asymptomatic latency Again neurosyphilis is three times as common and cardiovascular syphilis twice a common in men as in women The female sex hormones may play some role in the e differences since the course of experimental syphilis in th rabb t can b favorably influenced by the a lministration of estro en

The Influence of Imm nity on the Course of the Disease—The spontaneous course of untreated syphilis may vary between the extremes of a compl te cur " and a fatal termina t on Most often however the patient exhibits alternating periods of activity or latency and these se m dependent upon the state of the immun ty mechanisms

In the classical course of syphilis wh ch is more conspicuous by its absence than its presence the disease is initiated by an invasion of the body tissues with the spirochetes The era of *incubation* may last for ten to s xteen days and it is followed in some but by no means all persons by the appearance of the *primary les on* There is no accurate m thod by which it can be determined whether the chancre failed to develop or as in women passed without observation

Th *chancre* of syph lis teems wit sp rochetes and presumably stimulates tissue im mun ty a concept which led older phy cians to withhold active tr atment until the secondary eruption had put in its appearance The chancre is usually followed for a period of six weeks to six months by an *e a of laten y* befo e the *secon lary rashes* become man f st These les ons like the chancre contain myriads of spirochetes and presumably stimulate anew the tissue immunity so that there follows *another and longer period of latency* wh h may last for years or forever This final period of latency h s three po ible outcomes Spontaneous cure is exper enced by perhaps a third of the affli ted cl ni al cure with a pers stent pos tive serology is seen in another third and the remain ler of the affl cted develop visceral les ons usually cardiovascular or neurologic

It is important from the standpoint of practical therapy to differentiate between *early latency* and *late latency* The early period of lat ncy spans the first four or five y ars following the actual acquisition of the infection It is hypothecated that th tissue immunity mechanism is still being built up and hen e is capable of alteration by therapeutic m asures In late latency there is a tro g likel hood that the parasite and host *have reached* an impasse in wh ch the patient has at least acco npl shed a stalemate with his assa lant Und r these circumsta ces act ve treatment holds little promise *and some threat.*

This broad concept of the progression and course of syphil s has not been entir ly proved but its und rstand ng is essential to the practical management of many of the pr blems that present themselves to the physician during his exper ences with inf cted pati nts Again t the complete acceptance of the hypothesis is the fact that a *very large percentage*

realm of possibility that the disease could be eradicated by educational methods adequate legislation and competent administration The compulsory serologic examination as a premarital precaution and during pregnancy represents one great step in the right direction but unfortunately these measures apply only to those who adhere strictly to the standards of monogamy inherent in the marriage code

INDIVIDUAL PROPHYLAXIS

Until a Utopia is firmly established the best that can be accomplished with those who indulge in sexual intercourse outside of the holy bonds of matrimony is instruction in *venereal prophylaxis* (p 3122) Genital infection can be prevented by the use of a *condom* Whether or not this device is employed the genitalia and adjacent parts should be *washed thoroughly* with soap and hot water within one hour after intercourse After this any of the ointments containing approximately *33 per cent calomel* are applied vigorously to the male organ Females should use a vaginal douche of *1 2000 bichloride of mercury* but the protection afforded by this device is relatively minimal

Prophylactic Chemotherapy—We believe in instituting specific therapy for those patients known to have been exposed to infectious syphilis The simplest device *is a course of penicillin giving intramuscular* injections of 20 000 to 40 000 units at three hour intervals day and night until at least 1 200 000 and preferably 2 400 000 units have been delivered If routine conservative treatment is employed the course may be divided in half depending upon the clinical and serological developments If intensive treatment is utilized it is sufficient to administer a total of 500 to 760 mg of mapharsen

PRELIMINARIES TO TREATMENT

The treatment of infectious syphilis constitutes a problem so formidable that preliminary investigations and conversations are required before the actual administration of the curative drugs

The patient is to be told the *nature of the affliction* immediately after the diagnosis has been ascertained either by darkfield examination the serological tests or both He must be made acquainted with the general details of the plan of therapy For penicillin or intensive arsenotherapy hospitalization is urged for a period of 8 to 10 days *If conservative treatment* is to be employed he is told that he must expect to come to the doctor s office at regular intervals for 6 to 18 months At each visit he will receive an injection from which he may have local or systemic immediate or delayed toxic reactions The cost of his treatment is an appreciable percentage of the income of the average citizen hence he must be ready and prepared to make a significant economic sacrifice in order to regain his health

The patient must be told further that the alternative to complete treatment is the danger of chronic illness and perhaps death despite the apparently negligible present manifestations He must be warned that inadequate treatment is often worse than no treatment at all and that interrupted or intermittent therapy considerably lessens the chance for cure

If *ambulatory treatment* is taken the patient must also realize that

Clinical Manifestations

Syphilis may manifest itself in almost every organ and tissue of the body At each site a variety of different pathological lesions may be produced

The commoner proven clinical manifestations of syphilis are listed in Table 22 a more complete description of each of which is found in an



Fig 48 Clinical manifestations of syphilis The primary lesion (chancre) *A* and *B* Penis *C* Lip *D* Vulva *E* Anus *F* Face in child infected by parent

appropriate section At risk of repetition the practitioner again is warned against the conclusion that any disturbance in the Wassermann positive patient is necessarily luetic The syphilitic has sinusitis tuberculosis or malignant lesions in the same proportions as his serologically negative fellow

to the community the patient and himself to insist upon hospitalization We favor supplementation with intramuscular bismuth

Our second choice in syphilotherapy is *Five Day Treatment* also with bismuth supplementation Hospitalization is mandatory completion of therapy is assured satisfactory results are high but the treatment mortality rate of 0 25 per cent is a genuine threat The modifications of intensive arsenotherapy by the addition of hypertherm\ are for the specialist

If *ambulatory treatment* is required our preference is for the *Army method* which promises more certain completion than the Cooperative Clinic Group schedule Neither of these methods precludes the patient from mingling with the community during the period of infectivity

TREATMENT OF LATENT AND ASYMPTOMATIC SYPHILIS

The objective of treatment in latent or asymptomatic syphilis differs appreciably from that in the early forms of the infection In the latter it is the aim of the practitioner to destroy the invading organism Later his problem is directed at preservation of the health and life of his patient

The introduction of *penicillin* has greatly simplified the problem of the practitioner Using the technic previously described (p 340) he may give his patient the advantage of what appears to be optimum therapeutic activity at the cost of negligible toxicity there would seem to be no reason why the schedule cannot be repeated as often as deemed necessary

The alternative to penicillin therapy is a form of *ambulatory treatment* preferably that recommended by the *United States Army* We have always been skeptical concerning results of serologic tests in latent and asymptomatic syphilis We have never been convinced that the tests became negative any more frequently than would be anticipated in the spontaneous course of events as best illustrated in the Bruusgaard series (p 340)

THE TREATMENT OF NEUROLOGIC AND VISCERAL SYPHILIS

The special problems present in neurosyphilis are elsewhere discussed (p 1465) Our own experiences may be summarized by the statement that we have already seen extraordinary results from *penicillin* therapy and that *fever treatment* is a completely established procedure *Intraspinal methods* are cumbersome and quite futile they should be abandoned unless by intrathecal injections of penicillin

As in other forms of syphilis the introduction of penicillin *has greatly* clarified the problem of the treatment of *visceral lues* iodides are administered in the presence of the *gumma* supplementation by bismuth is justifiable *under all circumstances* We oppose the use of the intensive forms of therapy because of lessened patient resistance due to the ravages of the disease and the increased hazard of toxicology If all else fails however there is no reason why one of the methods of ambulatory conservative therapy cannot be inaugurated

SYPHILIS IN PREGNANCY

Despite the phenomenal success of intensive treatment by the method of the intravenous drip in pregnancy syphilis we are completely converted to the use of *penicillin* unless future developments reveal that this remedy has failed to live up to its early promise

the affliction rests wholly upon this examination since the serum remains clear for several important weeks

The technic of darkfield microscopy has been previously described (p 45) The actual execution of the technical steps offers no difficulty but the practitioner is warned that serious error may be made due to the presence of saprophytic spirochetes normally found in the mouth and in the region of the genitals (p 379) It is a wise precaution to have expert confirmation of the darkfield findings and to withhold any definitive statements until reasonable doubt has been dissipated

Serology—By far the most useful serodiagnostic test is the *Wassermann reaction* for syphilis This and the confirmatory flocculation tests by the methods of *Kahn Mazzini Hinton* and *Kline* often pose difficult problems for the practitioner to elucidate

The Interpretation of Negative Serologic Findings in Syphilis—*Completely negative serologic findings do not preclude the presence of syphilis* They are the expectancy in the *primary seronegative stage* and the blood is also likely to be clear in late lues of the visceral and nervous systems

The clinician interprets negative findings as an indication that antibody is not demonstrable He does not assume that the negative test precludes the possibility of clinical syphilis

The Interpretation of the Positive Wassermann Test—The practitioner should never accept an unconfirmed positive Wassermann test When a positive report reaches him he should take blood in triplicate The specimens are to be sent to *three* separate laboratories at least one of which performs the standard Wassermann test according to the provisions laid down by the United States Public Health Service Not until all of the reports have been received should the serologic diagnosis be discussed with the patient The clinician must be assured that the positive test is technically correct and confirmed before entering into conversation with the patient

The positive Wassermann test is presumptive evidence of the presence of syphilis Nevertheless there are *exceptions* and a *false positive* result may be present in *chicken pox malaria pneumonia leprosy meningitis infectious mononucleosis vaccinia rat bite fever relapsing fever atypical pneumonia lupus erythematosus pinta* and *frambesia tropica*

The established presence of syphilitic antibody does not necessarily mean that the patient is suffering from syphilis Syphilis may exist in a latent stage The patient may be suffering from some other condition that is wholly unrelated As in every other type of laboratory diagnosis the final interpretation rests with the clinician and his judgment is based upon his clinical findings and his experience

It is variously estimated that the incidence of positive serologic findings ranges from 10 per cent in the population as a whole to 50 per cent among certain groups notably the underprivileged laborers of the south

In view of the relatively high incidence of positive serologic findings the clinician must ever be on the alert to appreciate the presence of other clinical manifestations in individuals who happen incidentally to have positive serology

The Interpretation of Questionable Serologic Findings—Between the

Epidemiology—Yaws is transmitted through the discharges from skin lesions Infection may occur through body contact or through infectious fomites such as clothing or bedding, and may also be transmitted by insects such as flies Poor sanitation overcrowding and a lack of protective clothing favor the spread of the disease It is not transmitted to the fetus in utero as is syphilis

Clinical Manifestations—The characteristic of yaws is the appearance of the crusted *ulcer* or *mother yaw* at the point of inoculation The site of the lesion is almost always extragenital After a period of incubation a firm red *papule* is seen which soon develops into the ulcerous eruption After a period of quiescence a *generalized papular dermatosis* appears and these papules like the mother yaw become converted into crusted ulcers



Fig 50—Yaws Secondary eruption in florid stage (Fiji Islands)

or moist papillomata At this stage of the disease the parasites are disseminated and there are systemic manifestations which include *malaise headache fever anorexia* and *joint pain*

The skin lesions tend to heal spontaneously though some form destructive ulcers such as the gangosa of nose and hard palate In contrast to syphilis mucous membrane lesions are uncommon and the heart and central nervous system are rarely afflicted

Diagnosis—In tropical countries where the disease is endemic the treponemes may be demonstrated in the skin lesion by the darkfield examina

completely negative and the completely positive blood there will be found a large number of individuals who give dubious or questionable reactions *to the tests* Thus the Wassermann reaction may range from 1+ to 3+ or the Wassermann complement fixation test may be completely negative and the Kahn or Kline precipitation test remain positive If the super sensitive tests such as the Kahn presumptive the Mazzini the Hinton or the Eagle types are employed many patients will be found to have a positive flocculation test with questionable or negative complement fixation

In treated syphilis it is well known for example that the Wassermann complement fixation test will become negative while the flocculation tests remain positive for a variable length of time The difficulties of the clinician are increased when he meets with this type of experience

The serologist maintains that the presence of the positive test indicates that somewhere sometime the specific antibody has been formed and is forming in the circulating blood The clinician must decide for himself what may be the clinical connotation of the serologic investigation On the one hand he must not treat the serum and ignore the patient Contrariwise he cannot afford to ignore the information that has been given him by the serologist

The Therapeutic Test—When the clinician is unable to determine definitely the interpretation of the positive serologic findings he should perform *the therapeutic test The patient is treated for the supposed syphilis and* the diagnosis is withheld until the effect of specific therapy is noted

See *Differential Diagnosis of Dermatoses of Genitals and Perineum* (p 290)

The Cerebrospinal Fluid —Irrespective of the stage of syphilis the practitioner owes it to himself and his patient to collect cerebrospinal fluid for a complete examination Unsuspected positive findings are encountered in innumerable instances of infectious syphilis as well as in early and late latency (p 336) The required tests include the *cell count* the chemical test for *globulin complement fixation* and *flocculation reactions* and the plotting of the *colloidal gold curve*

See *Cerebrospinal Fluid* (Vol IV)

Knowledge that the spinal fluid findings are positive before the institution of therapy assists the practitioner in the arrangement of his therapeutic program and also serves as a protection to him in the event his judgment is later criticized In the presence of abnormalities of the fluid the patient is given a guarded prognosis and the necessity for prolonged observation and treatment is accentuated

Neurological Status —The physical examination of the syphilitic must include definite information concerning *pupillary reflexes ankle and knee jerks* the *plantar reflex* and *fundus oculi* The development of any abnormality warns the practitioner of central nervous system involvement on occasions in long standing syphilis the neurological findings are pathognomonic after the spinal fluid and the blood have cleared of reagin

Chest Radiographs —Cardiovascular syphilis most often manifests itself as an *aortitis* (p 1025) Before instituting therapy the practitioner should obtain a *radiograph* of the chest and an electrocardiogram for purposes of present diagnosis and as a base line for guidance in later years

Epidemiology —Yaws is transmitted through the discharges from skin lesions Infection may occur through body contact or through infectious fomites such as clothing or bedding and may also be transmitted by insects such as flies Poor sanitation overcrowding and lack of protective clothing favor the spread of the disease It is not transmitted to the fetus in utero as is syphilis

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Diagnosis —In tropical countries where the disease is endemic the treponemes may be demonstrated in the skin lesion by the darkfield examina

* MacCallum, Textbook of Pathology

Toxicity —The toxic manifestations which may be encountered include the *Herxheimer reaction* which as in other forms of syphilotherapy consists of elevation of temperature and increase of the luetic manifestations such as swelling of the chancre deepening of the syphiloderms and more marked regional lymphadenopathy In addition *herpes* of the lips or genitals may appear These disturbances do not require discontinuance of therapy they abate or disappear usually within twenty four hours Beyond or apart from the *Herxheimer reaction* the patient under penicillin therapy may develop a mild *fever urticaria* or *pruritus* Occasionally *nausea vomiting* and *abdominal cramps* are noted probably due to impurities in the drug

Results —The results of penicillin therapy are first seen by the accomplishment of a *negative darkfield examination* within twenty four hours *Serologic tests* require two to four months to become completely negative as in intensive arsenotherapy next to be described Preliminary indications suggest that satisfactory results are obtained in more than 90 per cent of the patients with early syphilis Treatment failures consist of *serologic* and *clinical relapses* which occur most often between the third and fourth months An occasional patient is serum fast as occurs in all types of syphilotherapy Those with serologic or clinical relapses may be subjected to retreatment the serum fast individual is best given chemotherapy with or without hyperthermy

In the *later forms of syphilis* penicillin therapy gives equally great promise Demonstrable favorable effects have already been noted in early asymptomatic neurosyphilis acute syphilitic meningitis paresis tabes and meningovascular neurosyphilis Serological tests are favorably affected but not completely cleared in late syphilis Gummatous lesions heal in twelve to forty six days The results of penicillin therapy do not seem to be affected one way or the other by previous treatment using other methods

The treatment of *neonatal* and *pregnancy syphilis* also has been followed with amazing success both for mother and child Preliminary results indicate that the infection is suppressed in most of the mothers miscarriages and stillbirths are averted neonatal deaths are prevented and infants are born healthy

Those children who are born with active evidences of the disease their mothers not having been treated with penicillin are also benefited *Late neonatal syphilis* responds with variable but generally satisfactory results

Combined Treatment —There would seem no reason why penicillin therapy cannot be combined with other forms of treatment *Bismuth* for example may well be given in conjunction with the remedy without risk of significant increase in toxicity Efforts will be made undoubtedly to observe the combined effects of *penicillin and arsenic* and *penicillin and fever* It would be our current opinion that the inclusion of forms of therapy with inherent toxicity should be reserved for those patients who fail to respond to penicillin alone or at most to penicillin and bismuth

Evaluation —The present status of penicillin therapy may be summarized as follows In favor of its utilization is its absence of significant toxicity and its already great promise for effective clinical results Against

quently persist The response is more rapid than would be seen in lues but the coexistence of the two diseases adds considerably to the confused state



Fig 51 —Secondary lesion or pintid on right cheek *

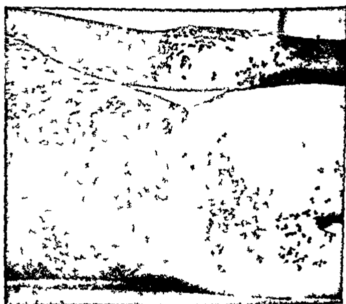


Fig 52 —Late pinta—areas of complete depigmentation of skin †

of the clinical manifestations Penicillin therapy merits clinical trial as in other treponematoses

* Mackie Hunter and Worth Manual of Tropical Medicine

† Courtesy of Dr Howard Fox

reasons that are not clear these complications have not been encountered to an appreciable degree A few instances of an increase in the icterus index have been recorded but these have been subclinical and transitory

The great risk of intensive treatment is relative to *toxic encephalopathy* This complication is evidenced in approximately 1 per cent of the patients Of those afflicted one in four will succumb the overall treatment mortality being 0 25 per cent The complication is more frequent in women than in men It seems to occur more often in alcoholics than those who are soberly inclined There are evidences that it occurs with undue frequency in women who are menstruating or about to menstruate Hence it is our present attitude to take steps to avoid the treatment in alcoholics and at the menstrual epoch

The *symptoms* and *signs* of toxic encephalopathy are elsewhere described (p 124) *Treatment* of the reaction consists in the immediate cessation of the administration of arsenic The drip however is kept on and 5 per cent dextrose in saline is continued A lumbar tap is done for diagnostic purposes and to relieve increased pressure We have obtained no helpful assistance from injections of sodium thiosulfate thiamine chloride nicotinic acid and cevitamic acid either singly or in combination though there is no reason why these cannot be added to the drip It has seemed to us to be most important to sedate the patient and prevent convulsions and this is best accomplished by adding paraldehyde or a soluble barbiturate to the infusion injecting the drug by hypodermic into the rubber tubing a few inches above the needle Hypertonic sugar solution in the form of 50 per cent sucrose may have some beneficial effect but remarkable detoxification is reputed to the anti lewisite preparation BAL (p 767)

Peripheral neuritis which constituted a real menace in the original intensive treatment experiments when neoarsphenamine was used has become a negligible problem since mapharsen was substituted

Care of the Patient During Treatment—The intensity of the treatment methods for syphilis requires that the physician take utmost precaution in the preliminary examination and in the surveys both during and after therapy

With intensive treatment when the patient is institutionalized it is a wise precaution to obtain a specimen of *spinal fluid* after the treatment has been completed and to get a *teleroentgenogram of the chest* for comparative purposes at a later date The daily examinations include a *full blood count* including platelets before and during the first day of treatment since any significant change in the erythrocytes leukocytes or thrombocytes calls for immediate cessation of arsenic injections The *urines* are examined each morning and should evidences be present of hepatic or renal irritation treatment is discontinued

Evaluation—Intensive arsenotherapy by the intravenous drip method produces negativity of the darkfield examination within twenty four to forty eight hours serologic reversal occurs between the second and fourth months sometimes earlier and occasionally later Seronegativity is accomplished in 85 to 90 per cent of cases in early syphilis The failures consist of serologic and infectious relapses and an occasional example of fastness Retreatment is available for serologic and infectious relapses by which the percentage of satisfactory results exceeds 90 per cent and approaches

are rarely done under proper conditions The importance of these isolated clinical occurrences is the evidence that they bring to bear on the actual state of symbiosis and invasiveness of the fusiform bacillus and the Vincent spirochete

In the few reported cases the source of infection seemed to have been a Vincent pharyngitis or rat bite The development of symptoms was rapid and characterized by *fever prostration headache myalgia* and *migratory arthritis* The affected joints were red hot swollen and very painful The course was protracted and relapses were frequent There was no leukocytosis and systemic therapy was directed at specific measures by the injection of the *arsenicals* The therapeutic results unfortunately were not striking

GINGIVOSTOMATITIS (TRENCH MOUTH)

See *Diseases of the Mouth* (p 1698)

ULCEROMEMBRANOUS ANGINA (VINCENT'S ANGINA)

See *Pain in the Throat* (p 2071)

BRONCHOPULMONARY FUSOSPIROCHETAL INFECTIONS

See *Diseases of the Respiratory Passages* (p 2210)

GANGRENOUS BALANITIS

See *Diseases of the Male Reproductive Organs* (p 2456)

TREATMENT

The first principle of treatment in fusospirochetal infection involves the correction or eradication of local and systemic predisposing causes that make possible the growth of these saprophytic organisms Whether or not an obvious local factor is easily demonstrable as in trench mouth the practitioner is remiss in his responsibilities if he does not seek the possible presence of some profound systemic disturbance particularly *leukemia agranulocytosis* or *avitaminosis* *No amount of specific therapy can accomplish any significant benefit so long as there are present local or systemic factors which provide gangrenous tissue upon which the organisms thrive*

Vitamin Therapy—Because of the frequent superimposition of fusospirochetal infection upon subclinical scurvy or pellagra the liberal administration of vitamin C and vitamin B complex has been enthusiastically advocated in the management of all the Vincent infections Vitamin C is administered as *ascorbic acid* 0 5 gm ($7\frac{1}{2}$ grains) twice daily and the *B complex* is provided as 15 to 30 gm (4 drams to 1 ounce) of *whole yeast* with the addition of 200 to 300 mg (3 to 5 grains) of *niacin* given in divided doses throughout the twenty four hours of the day

Arsenotherapy—The arsenical drugs do not have the specificity for fusospirochetal disease that they possess in the treatment of syphilis It is our opinion that nothing is accomplished by local application and if any reliance can be placed upon arsenotherapy the drug should be given as *mapharsen intravenously* in doses of 60 mg (1 grain) every second or third day for three or four injections Certainly this procedure should be followed in bronchopulmonary infections that are not based upon an under

venous injections of mapharsen Injections are given on the first third fifth and eighth days It is best to use a probatory minimal dose of 30 to 40 mg (1/2 to 2/3 grain) and increase if all is well to the full dose of 60 mg (1 grain) as soon as possible

The 60 mg (1 grain) doses of mapharsen are continued twice weekly thereafter for eight weeks and in the sixth seventh and eighth weeks bismuth injections are added as later described

The course of twenty mapharsen injections is repeated from the *fourteenth to the twenty third week* from the *thirtieth to the thirty ninth week* and then finally ten doses are given between the *forty eighth and the fifty seventh week* making a total of seventy intravenous injections in all If arsphenamine or neoarsphenamine is used the injections are given

TABLE 23—AMBULATORY CONSERVATIVE TREATMENT OF SYPHILIS (COOPERATIVE CLINICAL GROUP)

	Mapharsen	Bismuth (0 2 gm Injections)
First day	30 mg	0
Third day	40 mg	0
Fifth day	60 mg	0
Eighth day	60 mg	0
2nd to 5th week	2 60 mg injections weekly	0
6th to 9th week	2 60 mg injections weekly	1 weekly
9th to 13th week	0	1 weekly
14th to 23rd week	60 mg twice weekly	0
24th to 29th week	0	1 weekly
30th to 39th week	60 mg twice weekly	0
40th to 47th week	0	1 weekly
48th to 57th week	60 mg twice weekly	0
58th to 6 th week	0	1

weekly and are fewer but the schedule is much the same At least forty arsphenamine injections are given using an average dose of 0 4 gm (6 grains) and at least 50 injections of neoarsphenamine are given using an average dose of 0 6 gm (9 grains)

Bismuth —The intramuscular introductions of *bismuth salicylate* are inaugurated at the sixth week A dose of 0.2 gm (3 grains) is employed and a course of *eight injections* is given at *weekly intervals* The first two of these injections overlap the arsenical administration and the remainder are given during the first vacation from mapharsen

At the *twenty fourth week* the bismuth injections are resumed and *six* are given at weekly intervals this period corresponding to the second mapharsen vacation At the fortieth week, during the third mapharsen

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mice can be infected by subcutaneous injection of infective material and in their blood and viscera the spirochete can be demonstrated in great numbers Guinea pigs are resistant to the infection

Epidemiology—Relapsing fever is common in eastern Europe especially in the Balkans, where it occurs in epidemic form In Africa relapsing fever ranks next to prevalence to malaria and sleeping sickness In India the disease is also common

Louse borne Fever—In the United States epidemics of *louse borne relapsing fever* occurred in the eastern seaports during the Nineteenth Century but since that time only



Fig 53—Borrelia recurrentis in blood smear

rare sporadic cases have occurred in the eastern part of this country On the other hand *tick borne relapsing fever* occurs with some frequency in California and Texas and has been reported as well in Colorado Arizona and Kansas It al o occurs in Central and South America

Like typhus relapsing fever is a disease whose spread occurs during colder months of the year when people are crowded together without means of maintaining personal cleanliness In time of war and famine louse borne relapsing fever becomes epidemic Epidemic typhus and relapsing fever sometimes occur together (as they d d in Serbia during World War I) since they are both louse borne

Tick borne Fever—Tick borne relapsing fever is endemic in regions where various species of ticks are prevalent as in Central Africa and in western United States The tick borne

* Courtesy of Sharp and Dohme Seminar May 1944

plemented by weekly intramuscular introductions of the bismuth the patient thus concluding with both drugs in the same manner in which treatment was begun

Results—The preliminary reports of the results of Army treatment indicate minimum toxicity no mortality and more than 85 per cent satisfactory results

CRITERIA OF CURE

It is exceedingly difficult to assert with any degree of assurance that syphilis is cured Certainly the undernoted criteria constitute minimal requirements for safety

1 *Repeated serological observations* using routine and supersensitive tests have been completely clear for a period of at least one year
2 At least *two spinal fluids* have been taken at three to six months intervals and all tests are completely normal
3 *Physical examination* reveals no abnormality after particular focus upon the aorta and nervous system

TABLE 91—ACCELERATED AMBULATORY TREATMENT FOR SYPHILIS (UNITED STATES ARMY)

Weeks	Mapharsen (60 mg Injections Per Week)	Bismuth Salicylate (0 gm Injections Per Week)
1 to 5	2	1
6 to 10	2	0
10 to 17	0	1
17 to 22	2	0
2 to 26	2	1

MANIFESTATIONS OF TREATMENT FAILURE

Failure of treatment becomes manifest in several ways relative to the serologic or spinal fluid examinations and clinical characteristics These unhappy eventualities may be summarized as follows

1 The serum becomes *Wassermann fast* by which is meant that the positive test shows no alteration
2 The patient has a *serologic relapse* by which is meant that the Wassermann test les s and then reverses and once more is positive
3 The patient develops an *infectious relapse* or chancre redux" In this condition an open sore develops at the exact site of the original lesion This new ulcer again teems with spirochetes and is highly infectious Infectious relapse is always associated soon or late with Wassermann positivity either fastness or a reversal
4 With or without clearing of the blood the *spinal fluid gives evidence of involvement of the central nervous system* (p 3734) There may be pleocytosis increase of globulin seropositivity or the definitive changes in the colloidal gold curve (p 3736)
5 With or without serologic and spinal fluid alterations the patient shows clinical manifestations of cardiovascular or neurological syphilis

PREVENTIVE TREATMENT

The prevention of syphilis is a public health problem of unparalleled importance medically socially and economically It is entirely within the

Diagnosis

The diagnosis of relapsing fever is simple in an epidemic and is suggested in sporadic cases by the temperature chart

During the febrile phase it is sometimes possible to establish the diagnosis definitely by demonstrating the spirochete by darkfield examination of the blood or by the examination of fixed blood smears stained by the Wright method If these tests are negative blood from the patient is injected into mice and the animals are examined after forty eight hours The spirochetes multiply rapidly in these animals and can then be demonstrated by darkfield examination (p 46)

Since the practitioner rarely encounters relapsing fever it is well for him to communicate with the United States Public Health Service for further advice and assistance Specific complement fixation and agglutination tests have been reported

Treatment

The *arsenicals* have a specific curative effect on relapsing fever A single large dose given at the beginning of a febrile attack may be sufficient to alleviate symptoms If a recurrence is experienced the dose is repeated at the beginning of the second paroxysm As with other uses of arsenotherapy mapharsen 0 04 to 0 06 gm (⅔ to 1 grain) is the preparation of choice

Penicillin therapy already has established itself as the treatment of choice in both tick borne and louse borne varieties of relapsing fever It has replaced arsenotherapy because of its negligible toxicity particularly in the presence of jaundice and because of its proven efficacy

Best results are obtained if penicillin therapy is initiated at the very first manifestation of an attack The antibiotic may be given in solution using 40 000 units every three hours for a total of 2 400 000 to 5 800 000 units or 300 000 units of the oil wax suspension may be deposited twice daily for five to seven days (p 106) If recurrence is experienced there need be no hesitation in repeating the doses of penicillin

INFECTIOUS JAUNDICE (WEIL S DISEASE)

Infectious jaundice is a specific febrile disease due to infection with the spirochete *Leptospira icterohaemorrhagiae* and characterized by involvement of the liver and kidneys It is to be distinguished from catarrhal or camp jaundice the etiology of which is unknown

Infectious jaundice was first recognized as an entity by Weil in 1886 and in 1915 Inada discovered the causative agent and noted its frequent presence in *rats* Weil s disease is of worldwide distribution Many cases have been reported from western European countries especially Holland England and Scotland It occurred among troops on the Western front during World War I It is quite common in Japan and the East Indies In the United States not many cases have been recognized but in recent years there has been increasing interest in the disease

Closely related to Weil s disease are several leptospiroses of minor importance These include Seven Day Fever (Autumn Fever Pseudo

he is an infectious menace for perhaps the first three weeks following the initiation of treatment The danger is not only from sexual intercourse but may result equally from lesions of the other mucous membranes and skin Spirochetes from oral ulcers are a threat not only from direct contact but from indirect contact with drinking glasses silverware from kissing and from clothing

Because of the long incubation period of the disease the patient must be asked to warn contacts If he is married the wife should be told for her protection If the afflicted individual is at all conscientious other mem bers of the household had best be notified If the patient is unwilling to cooperate he should be informed that infectious syphilis is a reportable disease and that he or she is subject to the regulations of the local Public Health officials

The physician should attempt to learn the possible source of the infec tion so that the reservoir may be attacked by the private practitioner if possible or by public health officials if necessary

The preliminary conversation also is concerned with problems of *hygiene* and accessory forms of *nonspecific treatment* We favor the con tinuance of the *normal diet* correcting obvious deficiencies and imbalances We do not believe that reactions are cut down by high or low protein feedings or the use of excessive amounts of carbohydrates and starches Unless the patient has obvious evidences of avitaminosis *accessory vitamin administration accomplishes nothing* relative to the protection against toxic manifestations though many advocate the generous administration of *cevitamic acid* (p 627)

We do not oppose the continuation of *smoking* in moderation though older syphilologists have warned that the use of tobacco predisposes to oral lesions Our experiences tend to show that *excessive drinking* increases the toxicity in massive dose arsenotherapy and we avoid the immediate institution of the method in alcoholics and those who have been on a recent alcoholic bender We are not opposed however to normal and moderate drinking

Persons who are to receive bismuth and mercury should have their *teeth* cleaned prophylactically since stomatitis is more apt to occur in those who have infected gums and loosened teeth

There is some suggestion in intensive methods of treatment that reactions occur more often in *women* and more commonly if treatment is given during a *menstrual period* Consequently it is wise if possible to avoid injections during this epoch

As to sexual *intercourse* with ambulatory treatment this should be forbidden for at least six months after which a condom should be worn for at least another year If the Wassermann is negative at the end of that time normal insertion may be practiced With penicillin or five day treat ment the same precautions should be exercised since the infectious relapse which occurs in somewhat less than 10 per cent of the patients is com monly experienced at a critical period that approximates the twelfth week of the disease

TREATMENT OF EARLY SYPHILIS

We have already committed ourselves to the choice of *penicillin* in the treatment of infectious syphilis We believe that the practitioner owes it

ent in 80 per cent of severe cases but in more than half of mild cases it is absent As an example in the variations of severity of Havens 7 cases in Philadelphia one died and one other required hospital care 2 spent several days in bed and the other 3 were ambulatory Only 2 of the patients were jaundiced

Prognosis

The case fatality varies in different areas and at different times from 4 to 50 per cent Schuffner in Holland reported a case fatality rate of 10 per cent among 452 cases He further stated that without jaundice the disease is almost never fatal Among the jaundiced cases the mortality in his series has declined from 32 per cent to 16 per cent over a period of years



Fig 55—Secondary appearance of the wound in rat bite fever note black crust covering a chancre like indurated area surrounded by small vesicles

This may be the result of lessened virulence of the organism or the result of extensive use of serum therapy The uremic and meningeal forms of the disease still carry a high mortality

Diagnosis

In the *pre icteric stage* the important symptoms are the abrupt onset with myalgia particularly of the calf muscles the conjunctivitis chills

Courtesy of Sharp and Dohme Seminar May 1944

One of the outstanding characteristics of five day treatment has been the remarkable response of mother and child to intensive arsenotherapy the results in fact have been successful beyond all expectations The method is of the most particular value in those unfortunate women who are infected with primary syphilis in the last months of pregnancy Here rapid and complete destruction of the spirochete is essential for mother child and medical attendant and the rapidity of the method peculiarly meets the therapeutic indications

Although at present only preliminary results of therapy are available the penicillin effect on mother and child in pregnancy syphilis is phe nomenal A course of treatment lasting eight days in which 2 400 000 units are given in the manner previously indicated (p 340) suppresses the infection in most of the mothers averts miscarriages and stillbirths prevents neonatal death and permits of the delivery of a healthy infant The price of this in terms of toxicity is negligible

TREATMENT OF PRENATAL AND CONGENITAL SYPHILIS

Routine conservative and intensive forms of arsenotherapy are available for the newborn infant with congenital syphilis Injections may be made into the *jugular veins* or the *anterior longitudinal sinus* approached through the fontanelle Advocates of *intensive treatment* employ a total dosage approximating 80 mg ($1\frac{1}{4}$ grains) of mapharsen For routine therapy the individual dose should be slightly less than 1 mg ($\frac{1}{64}$ grain) per kilogram or 2 mg ($\frac{1}{3}$ grain) per pound of body weight The treatment of prenatal syphilis with penicillin may be initiated in utero or if neces sary after birth The results of the administration of the antibiotic agent to the mother have already been indicated Begun early and completed according to schedule the syphilitic mother should be delivered of a healthy child However should the infant reveal any evidences of neonatal infection penicillin injections may be continued or initiated A suggested total unitage approximates 20 000 to the pound but there would seem to be no reason why increasing amounts should not be utilized Thus the new born might easily tolerate 10 000 units given every three hours day and night for the first two weeks of its life The total delivery would thereby approximate one million units which should definitely insure an optimum therapeutic result In late neonatal syphilis the results cannot be expected to equal those obtained in early infection Nevertheless preliminary reports indicate that clinical improvement may be anticipated and dimin ished positivity but not complete clearing of the serology may be effected

FRAMBESIA TROPICA (YAWS)

Yaws is a chronic specific infectious disease that is seen almost exclu sively among Negroes in certain tropical countries such as Haiti It is a highly contagious but not venereal affliction and attacks both sexes and all ages but is most commonly seen in children See Fig 50

Etiology—The causative organism in yaws is the *Treponema pertenue* This spiro chete is not only morphologically indistinguishable from the *Treponema pallidum* of syphilis but the complement fixation and flocculation tests for the luetic infection are also *positive* in frambesia Indeed the similarity between the two diseases is so close that there are some who believe that yaws is a modified form of syphilis and group the various syndromes as manifestations of *treponematoses*

ferent organisms both of which are carried by rodents The *Spirochaeta* or *Spirillum minus* produces *sodoku* the type of disease most frequently seen in Japan The *Streptobacillus moniliformis* is the causative agent of *Haverhill fever* the variety observed in the United States

Sodoku

Sodoku is common in Japan and has also been reported in many countries throughout the world In the United States only about 125 cases had been reported up to 1940 (Fig 55 p 362)

Etiology—*Spirillum minus* naturally infects *wild rats and mice* and is also pathogenic for the guinea pig The organism is a tightly coiled spirochete with a relatively rigid body It has one or more flagella at each pole and moves very rapidly in darkfield preparations

Clinical Manifestations

Man is infected by the bite of rodents which are the natural hosts of the organism The *incubation period* varies from five to forty days but is usually less than ten days The rat bite generally heals during the incubation period The onset of symptoms is sudden with *headache nausea* and *chills* The temperature rises to 102° to 104° F and remains elevated for three or four days The scar of the local wound becomes inflamed and *lymphangitis* with *regional lymphadenitis* becomes evident During the height of the fever an eruption of large purplish *maculopapules* appear chiefly on the chest and arms After several days of fever the temperature returns to normal and the local lymphangitis and adenitis subside Then after several days *fever* and *local symptoms* recur These febrile bouts may persist for several months *Leukocytosis with eosinophilia* is noted and in a number of cases in which there were no evidences of syphilis the *Wassermann reaction became positive*

Diagnosis

Although spirochetes are present in the blood during the early febrile bouts they can rarely be found by darkfield examination Diagnosis is best made by injecting guinea pigs with blood or material aspirated from enlarged lymph nodes These animals are susceptible to the spirochete and die of the infection The organism can then be demonstrated by darkfield examination of the animal s blood or peritoneal exudate It should be remembered that these animals may be naturally infected already with *Spirillum minus* See *Differential Diagnosis of Eruptive Fevers* (pp 17 174)

Prognosis and Treatment

In Japan the mortality among untreated cases is reported to be 10 per cent By appropriate treatment this can be reduced to 1 or 2 per cent *Arsphenamine* or one of its derivatives has a specific curative effect Three injections bring about prompt cure but if less than that number are given relapses may occur Penicillin therapy has proved completely satisfactory and is the procedure of choice (p 106) The antibiotic is used as in the treatment of relapsing fever (p 360)

tion and the positive serology confirms the suspicion It is most difficult to exclude the presence of syphilis other than on clinical grounds Yaws is most frequently seen in young children testifying to its nonvenereal character but the laboratory data are wholly misleading and confusing

Treatment—As in the case of syphilis yaws is curable with injections of *penicillin* (p 340) Smaller dosages will probably suffice using 20 000 to 40 000 units every 3 hours day and night until a total of 1 200 000 or 2 400 000 units have been injected

As an alternative yaws may be treated by injection of the arsenicals *Mapharsen* is the preparation of choice as in syphilis (p 342) In primary and secondary infections three weekly intravenous injections of 60 mg of mapharsen are curative Tertiary yaws may require eight weekly intravenous injections With the first four bismuth subsalicylate (p 126) is given intramuscularly After the completion of arsenotherapy weekly bismuth injections are continued for another eight weeks If the Wassermann reaction remains positive the treatment course may be repeated if necessary

PINTA

Pinta is a specific infectious disease of *spirochetal origin* It is endemic in tropical and subtropical countries of the western hemisphere and is widespread in southern Mexico Central America and Colombia affecting large percentages of the population Pinta is also seen in the West Indies and other countries of the northern portion of South America It is known under various names such as tina carate azul boussarole guasarola puru puru and bejel cativi

Etiology—The *Treponema carateum* or *herrejoni* is the etiological agent in pinta The organism is indistinguishable from *Treponema pallidum* morphologically and in its serological reactions Many students of the disease believe that pinta is closely related to syphilis and group the affliction together with yaws as *treponematoses*

Clinical Manifestations.—Pinta is probably transmitted by the bite of a blood sucking insect or some other animal parasite A species of *Simulium* is suspected of vector activity The initial lesion appears at the portal of entry as a minute papule developing seven to ten days after inoculation After it has spread and the disseminating manifestations make their appearance the primary lesion cannot be distinguished from the rest of the eruption The specific skin lesions of pinta consist of *keratotic pintids* which occur on the extremities including the palms and soles There may be other associated areas of altered pigmentation The involved skin appears white or more characteristically has a *blue* or *grayish blue color* In addition to the eruption cardiovascular lesions and abnormalities of the spinal fluid have been reported in a small percentage of the afflicted thus closely simulating the infection of syphilis See Figs 51 and 52

Diagnosis—The diagnosis of pinta is established by demonstration of *Tr carateum* in material obtained from the typical lesion Positive Wassermann reactions are not observed prior to the development of the secondary lesions Only in advanced instances with marked pigmentations do positive tests approach 100 per cent

Treatment—Treatment with the *arsenicals* is successful in clearing the cutaneous manifestations though residual pigmentary abnormalities fre

CHAPTER 15

RICKETTSIAL INFECTION GENERAL CONSIDERATIONS

RICKETTSIAE are tiny bacillary bodies commonly found intracellularly in the intestinal canal of many arthropods Although several dozen varieties have been recognized only a few appear to be pathogenic for man

There seems to be no question but that rickettsiae are living organisms capable of reproduction They are extremely pleomorphic appearing at



FIG 6—A and B Electronic photomicrographs of *R prowazeki* C Yolk sac culture of *R prowazeki* D Agar tissue culture of *R orientalis*

times as coccoid and at other times as bacillary forms varying in length from 0.2 up to 2 0 microns They take the usual aniline dyes poorly but stain well with Giemsa Most rickettsiae do not pass through the pores of ordinary Berkefeld or other filters and in this respect they resemble bacteria On the other hand they cannot be cultivated except in the pres-

* Courtesy U S A Typhus Commission

tion and the positive serology confirms the suspicion It is most difficult to exclude the presence of syphilis other than on clinical grounds Yaws is most frequently seen in young children testifying to its nonvenereal character but the laboratory data are wholly misleading and confusing

Treatment—As in the case of syphilis yaws is curable with injections of *penicillin* (p 340) Smaller dosages will probably suffice using 20 000 to 40 000 units every 3 hours day and night until a total of 1 200 000 or 2 400 000 units have been injected

As an alternative yaws may be treated by injection of the arsenicals *Mapharsen* is the preparation of choice as in syphilis (p 342) In primary and secondary infections three weekly intravenous injections of 60 mg of mapharsen are curative Tertiary yaws may require eight weekly intravenous injections With the first four bismuth subsalicylate (p 126) is given intramuscularly After the completion of arsenotherapy weekly bismuth injections are continued for another eight weeks If the Wassermann reaction remains positive the treatment course may be repeated if necessary

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Courtesy U S A Typhus Commission

CHAPTER 14

SPIROCHETAL INFECTIONS BORRELIA LEPTOSPIRA AND SPIRILLA

Fusospirochetosis (*Borrelia vincenti*)
Relapsing Fever (*Borrelia recurrentis*)
Infectious Jaundice (*Leptospira icterohaemorrhagiae*)
Rat Bite Fever
Sodoku (*Spirillum minus*)
Haverhill Fever (*Streptobacillus moniliformis*)

FUSOSPIROCHETOSIS (VINCENT'S INFECTION)

A NUMBER of clinical conditions are encountered in which *fusiform bacilli* and *Vincent spirochetes* are regarded as etiological agents Among such entities are *gingivostomatitis (trench mouth)* *Vincent's angina* various *bronchopulmonary lesions* *gangrenous balanitis* and *septicemia* The etiological significance of the fusospirochetal organisms found in these conditions is not clear since some authorities deny that they have any primary relationship to the pathological processes and regard them as mere secondary invaders There is no question that these organisms are ordinarily of low or doubtful virulence and it appears probable that they cannot readily produce disease unless the vitality of the tissues has been lowered by some local or systemic cause

Etiology—The fusospirochetal organisms are anaerobic and as ordinary cultural methods are inadequate for their bacteriological growth identification is accomplished by morphological means Both organisms are demonstrable in great numbers in stained smears of membrane exudate sputum or other material obtained from patients with fusospirochetal disease To prepare a smear the membrane or ulcerated area is swabbed and the exudate is rolled on a clean glass slide It is fixed by drying and heating and stained with gentian violet, carbolfuchsin or methylene blue In such a preparation the *fusiform bacillus* is a rather long spindle shaped organism thickest at the center and tapering at each end varying in length from 7 to 15 μ The *Vincent's spirochete* is a long thin undulating organism from one to two times as long as the fusiform bacilli It stains poorly with ordinary dyes and is difficult to see even when present in great numbers It has been claimed that the spirochete and the bacillus represent different stages in the life cycle of the same organism but this view is generally discredited

CLINICAL MANIFESTATIONS

Under unusual circumstances the fusospirochetes are capable of producing a septicemia More often they are encountered in localized infections such as *gingivostomatitis* *ulceromembranous angina* *bronchopulmonary infection* or *gangrenous balanitis*

FUSOSPIROCHETAL SEPTICEMIA

In a few rare instances the fusospirochetal organism has been isolated from blood cultures by anaerobic methods though they were not seen on direct darkfield examination It is quite possible that many similar instances have gone unrecognized since anaerobic cultures are difficult to make and

Tissue Localization—Both in man and in experimental animals rickettsiae show a selective affinity for localization in mesothelial cells lining serous cavities (*tunica vaginalis* and *peritoneum*) and in the endothelial cells of blood vessels where they produce capillary thromboses and perivascular inflammatory reactions The rickettsiae of the *typhus* and *spotted fever groups* differ in their pathogenicity for rats and guinea pigs and can be further differentiated by the types of lesions they produce in these animals See Fig 56

Clinical Manifestations—Clinical disease results from infection with the organisms themselves since there is no evidence that they elaborate toxins The rickettsiae invade and multiply in large mononuclear tissue cells and the resulting inflammatory reaction is responsible for the symptoms of disease *Typhus* and *spotted fever* are both characterized by fever a cutaneous eruption and evidence of diffuse involvement of small blood vessels in the skin and viscera

Immunity Reactions and Therapy—Rickettsial infection stimulates the production of antibodies which can be detected in the host s blood serum by various technics These include *agglutinins complement fixing* and *neutralizing antibodies*

Recovery from rickettsial disease is followed in general by a durable *active immunity* similar to that which follows many of the virus diseases Artificial active immunization is now possible for *typhus* and to a limited extent for *Rocky Mountain spotted fever* It is not yet known how permanent or how effective artificial immunization will be in rickettsial disease but remarkable curative effects have been noted following the administration of para aminobenzoic acid (p 136) in typhus Rocky Mountain spotted and Tsutsugamushi fevers

lying blood dyscrasia. Under no circumstances should the arsenical be given when there is an agranulocytosis or an acute leukemia. The drug may be employed however with relative safety in the chronic blood dyscrasias.

Sulfonamide Therapy.—There is recent evidence to support the hope that sulfonamide therapy may prove of incalculable benefit in the treatment of fusospirochetal disorders. The drug of choice is *sulfathiazole* which should be given orally in 4 gm. dosage for two to six days in order to provide an adequate blood concentration. As with arsenical, the use of sulfonamide medication should be preceded and followed by careful studies of the hemogram. It is suggested that oral sulfonamide be regarded as the treatment of choice to be followed by arsenotherapy intravenously in the recalcitrant case.

Penicillin Therapy.—Penicillin therapy holds great promise in the fusospirochetoses. Local lesions after spraying and drying may be touched with solutions of the antibiotic in concentrations of 100 000 units per cc. *Supplementation with parenteral injections using 300 000 units in oil and wax twice daily for several days is mandatory unless the lesions are inconsequential.*

Other Measures.—Many other preparations have been advocated in the treatment of the Vincent infections. Some like *antimony* and *potassium tartrate fuadin* and *acetarsone* have considerable potential for toxicity and little specific activity to recommend them.

RELAPSING FEVER

Relapsing fever is an insect borne spirochetal infection that is widely prevalent in many areas of the world. In different regions of the world the spirochete bears different names and is transmitted by different vectors such as the *human louse* and various kinds of *tick*. Some of the common types of spirochetes and their vectors are listed in Table 25.

TABLE 25.—VARIETIES OF RELAPSING FEVER AND THEIR VECTORS

Disease	Spirochete	Vector
European relapsing fever	*Borrelia recurrentis* (*Spirillum obermeieri*)	Body Louse
Central African relapsing fever	*Borrelia duttoni*	Tick
North African relapsing fever	*Borrelia berberi*	Louse
Indian relapsing fever	*Borrelia carteri*	Louse
North American relapsing fever	*Borrelia novyi*	Tick

Relapsing fever is variously labeled "tifo recurrente," "fiebre recurrente," "febris recurrens," "fièvre récurrente," "Rückfallfieber," "Rückfalltyphus," "garapata disease," "spirillum fever," "famine fever," and "tick fever."

Etiology.—The strains of spirochetes in relapsing fever are morphologically identical. *Borrelia recurrentis* is 10 to [illegible]0 μ in length with four to ten open irregular coils and tapering ends. In fresh preparations it moves with an active corkscrew motion. It takes the usual bacterial stains as well as the Wright or Romanowsky stain used for blood smears. It can be cultivated on special media but this is not a practical procedure. Monkeys, rats and

during the act of biting humans The rickettsiae then get into the human blood stream through the bite wound probably as a result of scratching Since the disease is transmitted only when man and lice are closely associated epidemics occur under conditions in which sanitation and personal hygiene break down It is more prevalent in winter because people are crowded closer together during that time and wear heavy clothes in which lice can breed A completely deloused patient is noninfectious to his associates if they are also free of lice Although it is stated that the sputum of patients may be infectious there is as yet no definite evidence of this

Pathology—The gross pathological lesions of typhus are not distinctive The characteristic features of the disease are recognized only by microscopic examination of the tissues The lesion is essentially a proliferative reaction of the endothelial lining of arterioles and capillaries with surrounding perivascular round-cell infiltration Rickettsiae are present in the



Fig 57—Rash of typhus fever*

endothelial cells The findings are most prominent in the vessels of the skin central nervous system and myocardium Thrombosis of involved arterioles and capillaries results in the petechial and other hemorrhagic manifestations of the disease

CLINICAL MANIFESTATIONS

The *incubation period* of epidemic typhus fever varies from five to fifteen days Vague malaise may be present for a day or two but in most instances the onset is abrupt The initial symptoms are *chills* or chilliness *rise in temperature* and *intense headache* *Pains in the legs or back* *vomiting* and *constipation* are also present in the early stages of the disease The

* Courtesy of Eli Lilly and Company

disease is usually sporadic rarely epidemic In *Texas* 258 cases were reported from 1930-34 with no deaths In *California* 138 cases have been reported from 1930-38 In the latter state the disease occurs only in areas at an elevation greater than 5000 feet The tick which transmits the disease to man is a natural parasite of squirrels and other rodents which prefer to live at this altitude Both in Texas and in California the summer months are the periods of chief prevalence of relapsing fever

Pathology.—In fatal cases the characteristic finding is the enlarged spleen which contains miliary necrotic lesions laden with spirochetes Jaundice is present and hemorrhages in the skin and viscera occur Death is usually the result of complicating pneumonia.

Clinical Manifestations

The clinical features of relapsing fever are similar whether tick borne or louse borne There is a short febrile period lasting four to ten days which begins and ends abruptly This is followed in one to two weeks by a similar but milder paroxysm In the European type two or three relapses may occur in untreated cases whereas in the African type there may be as many as ten With each attack of fever spirochetes are present in the blood stream but in remissions they disappear from the peripheral

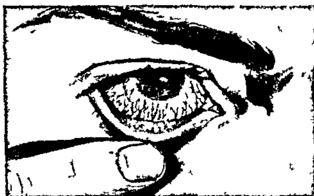


Fig 54.—Appearance of the eye in early Weil's disease (infectious jaundice)

blood and are present in the spleen Immunity develops during the course of the disease and probably accounts for the mildness of the successive attacks and the eventual self limitation of the disease In patients who are untreated the disease may last six to eight weeks

In the United States the disease resembles the European type clinically The onset is abrupt with *headache chills fever* and *vomiting* The fever lasts two to five days and then falls by crisis accompanied by profuse drenching sweats *Relapses* occur at irregular intervals of two to nine days A *rash* consisting of rose colored spots may be present on the trunk and extremities *Splenomegaly* is usual and *hepatomegaly* may also occur *Jaundice* appears only in severe cases *Albuminuria* is common casts frequent and hematuria rare The disease is accompanied by *leukocytosis* and in a variable proportion of cases *false positive Wassermann reactions* may be present

Prognosis

The case fatality rate is stated to be 2 to 5 per cent Among several hundred cases in the United States no fatalities have been reported

Courtesy of Sharp and Dohme Seminar Nov 1943

during a twenty year period revealed that 95 per cent occurred in foreign born individuals particularly in Russian Jews Zinsser was led to believe that Brill s disease was an imported form of classical European typhus which occurred as a recrudescence of the previous infection From typical cases of Brill s disease he isolated strains of typhus which behaved like the rickettsiae of epidemic or European typhus

Clinically, Brill s disease is identical with European typhus except that it is not louse borne and is much milder

DIAGNOSIS

In the presence of an epidemic the clinical diagnosis of European typhus is not difficult The characteristic sudden onset with headache and sustained fever suggests the diagnosis and the development of the typical eruption confirms the suspicion When the disease is sporadic diagnosis is more difficult and until the appearance of the rash other acute febrile diseases such as influenza malaria relapsing fever and typhoid fever may be simulated *Typhoid* has a more gradual onset and diagnosis can be confirmed by blood cultures and Widal test In contrast to typhoid fever, there is usually a leukocytosis of 12 to 15 000 cells per cu mm in typhus *Relapsing fever* and *malaria* both characterized by splenomegaly can be proved by examination of the blood for the specific causative agents (p 50)

European typhus fever must be distinguished from *murine typhus* and from the *spotted fevers* While there are characteristic differences in the severity and course of these diseases and in the character of the eruption the differentiation is best made by a combination of epidemiological and laboratory evidence Evidence of lousiness of the patient points strongly to European or Mexican typhus A history of tick bites points to spotted fever The presence of rats and the bite of rat fleas suggest endemic (American) typhus In general epidemic or European typhus is seen in Eastern Europe and as sporadic cases of Brill s disease in the large cities of eastern United States Spotted fever and endemic typhus are found widely distributed throughout the United States and it is in the differentiation of these two rickettsial diseases that laboratory aid can be most useful To avoid repetition it will be convenient to discuss the laboratory diagnosis of the typhus and spotted fever groups of rickettsial diseases together at this point

Weil Felix Reaction —During World War I, a variety of *proteus organism* was recovered from the urine of several patients with typhus fever Agglutinins for this organism developed in the patient s serum during the course of the disease leading to the belief that proteus was the cause of typhus When this theory was demolished by the finding of *Rickettsia prowazeki* it was considered that the intracellular rickettsial bodies were mutants of the proteus bacillus These theories have now been disproved and there is general agreement that proteus has no etiologic relation to typhus fever Nevertheless this unrelated organism is capable of being agglutinated by the serum of patients with rickettsial diseases and is thus an extremely valuable diagnostic aid The only explanation for the strange phenomenon is one advanced by Zinsser namely that proteus and rickettsiae have certain chemically similar fractions which give them antigenic similarity This is by no means unheard of in bacteriology since type B

Dengue) of Japan Malaya and Java Marsh or Swamp Fever of Central Europe and Russia and *Leptospira canicola* infection of dogs which may be transmitted to man

Etiology —*Leptospira icterohaemorrhagiae* is a tightly coiled spirochete 6 to 14 μ in length One or both ends are bent in a hooklike fashion Propulsion occurs by a rotary motion of the hook and progresses in the direction of the straight end The organism can be cultivated on Noguchi s medium and the membranes of developing chick embryos

Epidemiology —*Leptospira icterohaemorrhagiae* has been recovered in from 1 to 50 per cent of rats trapped in different parts of the world The highest incidence has been reported from Holland and Japan where human infection also appears to be most prevalent The rat may harbor the parasite throughout its life and apparently suffers no harm from it The organisms are discharged in the urine and feces and man is commonly infected by ingestion of water or food contaminated with infected rat urine or by contact of infected water with abrasions of the skin Laboratory infections have resulted from the bites of rats or by accidentally spraying cultures of the organisms in the conjunctivae A closely related strain of spirochete *Leptospira canicola* is found in dogs Infection of man with this organism may occasionally produce a clinical syndrome similar to Weil s disease

It has recently been recognized that the disease tends to occur among certain occupational groups It is particularly frequent among *bargemen sewer workers wharf men fish workers miners slaughterhouse workers and those whose occupation is in places infested with rats Trench warfare* such as occurred in World War I favors the production of the disease In Holland the fever occurs in the summer months among swimmers in the canal Recently seven cases occurred in the environs of Philadelphia among men bathing in a pool polluted with infected rat urine

Pathology —In fatal human cases the *liver* is slightly enlarged The hepatic cells have focal degenerative changes which are never as marked as in acute yellow atrophy The *spleen* is soft and slightly swollen The *kidneys* show degeneration and necrosis of the epithelium of the convoluted tubules with round cell infiltration and hemorrhages in the interstitial tissue Silver impregnation stains may demonstrate spirochetes in the liver kidney and other organs *Hemorrhages* in the skin subcutaneous tissue muscles and viscera are common

CLINICAL MANIFESTATIONS

The usual *incubation period* of infectious jaundice is six to twelve days The onset is abrupt with *fever chills headache vomiting* and *pains in the muscles* particularly the calves *Injection of the vessels of the conjunctivae* is a characteristic feature of the disease and Dutch clinicians regard this as a pathognomonic sign Fever varies from 102 to 104 F for three or four days and then falls toward normal In the second week of the disease there may be a second rise in fever lasting about a week before convalescence sets in (Fig 54 p 359)

Jaundice appears two or three days after the onset of the fever The *liver* is slightly enlarged and tender and the *spleen* is palpable *Neurological signs* or even *meningitis* may occur and the organisms have been recovered from the spinal fluid *Oliguria* with *albumin casts red cells* and *bile* in the urine is a characteristic feature of the disease *Azotemia* occurs in severe cases and death from *uremia* has been described *Bleeding* from the nose or rectum and *purpura* are seen in severe cases *Leukocytosis* up to 15 to 20 000 per cu mm is observed

The fullblown syndrome is observed in severe cases but from laboratory tests particularly agglutination reactions it has become evident that mild cases may occur without jaundice and the infection may be entirely subclinical It was found for example that 20 per cent of a group of sewer workers had agglutinins for *Leptospira icterohaemorrhagiae* without ever having had a recognized attack of the disease In Holland jaundice is pres

use and should prove useful in the diagnosis of the various types of rickettsial infection False positive Wassermann reactions may be obtained during the acute phases

PROGNOSIS

The case fatality of epidemic typhus has varied widely in different epidemics In Serbia in 1915 it reached 70 per cent and during World War I in Poland and Russia it was about 20 per cent In recent years the fatality rate in eastern Europe has been between 8 and 12 per cent The mortality rises directly in proportion to the age of the patient Death is very uncommon in children and in them the disease tends to be mild This is also true in general, for endemic typhus and for spotted fever In older persons death most often results from bronchopneumonia circulatory failure or involvement of the nervous system

In contrast to the severity of European Typhus *Brill s disease* has a negligible mortality

TREATMENT

Convalescent serum is said to ameliorate the severity of typhus but reports of its usefulness have not been consistent Zinsser prepared a *horse serum* against murine or endemic typhus and reported encouraging results from its use Experimentally it gave partial protection to guinea pigs infected with European virus but there has been no clinical report of its extensive use in this disease

While specific therapy for typhus fever has not yet been perfected there are evidences that this problem may be solved The rickettsiae are sensitive to *penicillin* as well as to other preparations such as *toluidine blue* and *forbisen* Successful individual case reports have been made following the use of *plasmochin atabrine* and *neoarsphenamine* The sulfonamides appear ineffectual but the severity of the illness and its span are decreased by the administration of para aminobenzoic acid with 25 cc of 5 per cent sodium bicarbonate After an initial dose of 4 to 8 gm (60 to 120 grains) successive doses of 2 gm (30 grains) are administered orally every two hours to achieve and maintain a blood concentration of 10 to 20 mg per 100 cc until the rectal temperature remains below 99 5° F for twenty four hours Drug toxicity is not observed except for nausea and vomiting (p 136) Digitalis and other cardiac stimulants appear useless or harmful and sulfonamides are added only when there are purulent complications The circulation is best supported with plasma infusions and a daily dose of 2 to 5 gm (30 to 75 grains) of sodium chloride

PREVENTION

The control of epidemic typhus requires the elimination and destruction of human lice Those in attendance upon the typhus patients must take extreme precautions to prevent contamination of their clothing by lice

Perhaps the most important forward step in typhus prevention has been the introduction of D D T the U.S Army s insect powder which effectually kills lice termites moths roaches bedbugs fleas Japanese beetles corn borers and other insect pests

D D T is *dichloro diphenyl trichlorethane* a compound harmless to man When D D T is mixed with talc or kerosene, it is deadly to insects

fever headache and sometimes signs of meningeal irritation These symptoms are common at the onset of many other infectious diseases but their persistence for several days and the failure of signs characteristic of a well recognized infectious disease to develop should suggest the possibility of Weil s disease Jaundice develops in only 50 per cent of all patients and physicians must be alert to recognize the disease in the absence of that sign

In the presence of visible *jaundice* a careful history should be taken with regard to possible contact with *rats* *Catarrhal jaundice* of the usual unknown etiology does not produce marked urinary abnormalities In the presence of albuminuria and casts with or without azotemia Weil s disease should be suspected and appropriate laboratory tests performed *Yellow fever* and *relapsing fever* may produce a clinical picture similar to Weil s disease but they are only found in restricted regions of the world

See *Jaundice Differential Diagnosis of* (p 1951)

Demonstration of Spirochetes—Spirochetes are present in the *blood* during the first week but after ten days they are no longer detectable and then appear in the *urine* where they may persist for as long as six weeks In the first week of the disease therefore the blood should be examined for spirochetes by *darkfield examination* and by *peritoneal injection* into guinea pigs less than six weeks old Should the animals die the organisms may be demonstrated in the lesions After the first week of the disease the centrifuged urine may be examined directly for spirochetes or injected into guinea pigs (p 46)

Agglutinins—Specific agglutinins develop towards the end of the first week of the disease reach very high titers in convalescence and may persist for as long as eight years The agglutination test is done by the macroscopic tube method or by a microscopic technic using living or killed suspensions of spirochetes A titer of 1 100 is present by the end of the first week and may eventually rise to as high as 1 1 000 000 Of the various laboratory procedures animal inoculation and serological tests are most reliable while darkfield examinations of blood and urine are least satisfactory and most difficult

Treatment

A *horse antiserum* has been prepared by repeated injections of cultures of *Leptospira icterohaemorrhagiae* This serum appears to have a favorable but not striking effect on the course of the disease The symptomatic treatment is that of any acute hepatic disease (p 1955) The treatment of azotemia is discussed elsewhere (p 2282) *Arsphenamine* and other arsenicals have proved ineffective in this disease and their use may be dangerous (p 192)

There is as yet no practical method of *active immunization* but the successful extermination of rats reduces and may eliminate the disease Penicillin therapy gives evidence in experimental disease of great therapeutic promise and should definitely be used by the practitioner as in the treatment of relapsing fever (p 360)

RAT BITE FEVER (HAVERHILL FEVER SODOKU)

The bite of a rat may be followed by a relapsing type of fever often accompanied by a dermatosis Infection may result from two widely dif

taminated by rat urine containing the rickettsiae *In the United States* the rat flea is the vector to man but *in Mexico* murine typhus spreads to man via the flea and then from man to man by human lice

CLINICAL MANIFESTATIONS

Endemic typhus follows the same pattern as European typhus but the disease is milder complications are rare and the case fatality rate is low The onset may be abrupt with *chills* and *headache* or more gradual. The *temperature* rises progressively reaching 102° to 105° F in three to six days It persists for about fourteen days and falls rapidly to normal The *rash* appears on the fifth day, usually on the chest and abdomen It may involve the whole body but generally spares the palms and soles It consists of rose or dark red macules which do not disappear on pressure The rash lasts from two to ten days and then fades rapidly *Nervous symptoms* are much less pronounced than in classical typhus Apathy alternating with irritability and insomnia is common but the profound stupor or delirium of European typhus is not seen Gangrene and other severe complications are rare or absent

DIAGNOSIS

In an endemic area an *acute infection* lasting two weeks with *headache prostration* and a *rash* suggests the diagnosis of typhus A *history of tick bite* favors the diagnosis of spotted fever The *Weil Felix reaction* makes the diagnosis of a rickettsial disease but does not exclude spotted fever In the future *complement fixation tests* will probably be most useful in separating the two diseases

PROGNOSIS

The fatality rate varies greatly with age In young individuals it is a benign infection In Alabama the case fatality has been less than 2 per cent in persons under the age of forty five from 5 to 7 per cent for ages forty five to sixty five and about 30 per cent for persons over sixty five years of age

TREATMENT

Endemic typhus fever is best treated with para aminobenzoic acid (p 136) After an initial oral dose of 4 0 to 8 0 gm (60 to 120 grains) maintenance doses of 2 0 gm (30 grains) are given at two hour interval with bicarbonate of soda until the patient has been afebrile for forty eight hours

PREVENTION

The prevention of endemic typhus in this country is essentially a problem of *rat extermination* While vaccines for *active immunization* may be of value in European typhus it would not seem worthwhile to embark on an extensive campaign of immunization in this country since endemic typhus is sporadic and mild

ROCKY MOUNTAIN SPOTTED FEVER

Spotted fever was first recognized in the Snake River Valley of Idaho and the Bitter Root Valley of Montana Long before the etiologic agent was discovered it was recognized that the disease was transmitted by ticks and until a dozen years ago it was believed that the disease was confined to the Rocky Mountain states Since 1930 however cases have been found

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In the presence of visible *jaundice* a careful history should be taken with regard to possible contact with *rats* *Catarrhal jaundice* of the usual unknown etiology does not produce marked urinary abnormalities In the presence of albuminuria and casts with or without azotemia Weil s disease should be suspected and appropriate laboratory tests performed *Yellow fever* and *relapsing fever* may produce a clinical picture similar to Weil s disease but they are only found in restricted regions of the world

See *Jaundice Differential Diagnosis of* (p 1951)

Demonstration of Spirochetes—Spirochetes are present in the *blood* during the first week but after ten days they are no longer detectable and then appear in the *urine* where they may persist for as long as six weeks In the first week of the disease therefore the blood should be examined for spirochetes by *darkfield examination* and by *peritoneal injection* into guinea pigs less than six weeks old Should the animals die the organisms may be demonstrated in the lesions After the first week of the disease the centrifuged urine may be examined directly for spirochetes or injected into guinea pigs (p 46)

Agglutinins—Specific agglutinins develop towards the end of the first week of the disease reach very high titers in convalescence and may persist for as long as eight years The agglutination test is done by the macroscopic tube method or by a microscopic technic using living or killed suspensions of spirochetes A titer of 1 100 is present by the end of the first week and may eventually rise to as high as 1 1 000 000 Of the various laboratory procedures animal inoculation and serological tests are most reliable while darkfield examinations of blood and urine are least satisfactory and most difficult

TREATMENT

A *horse antiserum* has been prepared by repeated injections of cultures of *Leptospira icterohaemorrhagiae* This serum appears to have a favorable but not striking effect on the course of the disease The symptomatic treatment is that of any acute hepatic disease (p 1955) The treatment of azotemia is discussed elsewhere (p 2282) *Arsphenamine* and other arsenicals have proved ineffective in this disease and their use may be dangerous (p 122)

There is as yet no practical method of *active immunization* but the successful extermination of rats reduces and may eliminate the disease Penicillin therapy gives evidence in experimental disease of great therapeutic promise and should definitely be used by the practitioner as in the treatment of relapsing fever (p 360)

RAT BITE FEVER (HAVERHILL FEVER SODOKU)

The bite of a rat may be followed by a relapsing type of fever often accompanied by a dermatosis Infection may result from two widely dif

marked on the extremities In the stage of its full development petechiae are present on the mucosa of the mouth and pharynx and on the palms and soles The petechiae may be accentuated by the application of a tourniquet and they do not disappear on pressure The full development of the eruption is complete in two or three days and is associated with some amelioration of muscular aching but the fever persists unabated In milder cases the eruption remains discrete At first it is rose red later darkening to take on a blue red or purple tint In patients who are more severely ill the petechiae increase in size and number until they become confluent purpuric areas may develop and the skin assumes a bluish mottled appearance The eruption persists during the febrile stage fading slowly as the temperature returns to normal It is followed by desquamation

Circulatory Manifestations—In the early stages of spotted fever the pulse tends to be of good volume and relatively slow in proportion to the temperature Later in the course it becomes more rapid A marked tachy-



Fig 58—Eruption of Rocky Mountain spotted fever

cardia with a small weak pulse indicates a failing circulation and is a feature of cases with poor prognosis

Other Manifestations—Marked *prostration* is a common feature of spotted fever *Mental confusion apathy* and *dullness* are usually present but delirium and coma may occur Convulsions are rare and in general mental disturbances are not as frequent or severe as in typhus

Muscle aches and *pains* are present throughout the illness and may be excruciating at times *Hyperesthesia* of the skin is a prominent feature of the illness The *spleen* is enlarged and tender Occasionally the *liver* is also enlarged and in severe illnesses *jaundice* may develop during the second week of the disease *Albuminuria* is regularly present *Leukocytosis* of from 12 to 15 000 per cu mm is the rule and a moderate *anemia* commonly develops

Cough is a characteristic complaint and *pneumonia* is the most common

Courte of Sharp and Dohme Seminar May 1942

Haverhill Fever

In 1914 Schottmuller described a *streptothrix* in the blood of a patient with rat bite fever In 1916 Blake isolated a similar organism from a fatal case of the disease In 1925 Levaditi named the same organism *Streptobacillus moniliformis* A year later in the course of a milk borne epidemic Place and his associates isolated an organism which they called *Haverhillia multiformis* It is now evident that these workers were dealing with the same organism to which the name *Streptobacillus moniliformis* may be applied Rats and other rodents appear to be the natural hosts of the organism (Fig 55 p 369)

Etiology—*Streptobacillus moniliformis* is a pleomorphic organism growing as chains of bacilli interspersed with beaded swellings Special med a and technics are required for the growth of this organism

CLINICAL MANIFESTATIONS

The clinical manifestations of Haverhill Fever due to *Streptobacillus moniliformis* resemble sodoku (p 364) with certain minor differences in symptomatology and course In Haverhill Fever the *onset* of symptoms is only one to three days after the rat bite and the signs of local inflammation are less marked Fever is intermittent in the bacterial infection but is not as regularly relapsing as in sodoku On the other hand *joint pains* and *arthritis* are more common in streptobacillus infection

In 1926 86 cases of rat bite fever occurred in Haverhill Massachusetts It was determined that the disease was *milk borne* and there had been no contact with rats on the part of the patients From the blood and joint fluid of patients an organism was cultured which was identical with *Streptobacillus moniliformis* It seems possible that milk had been contaminated by rats The Haverhill fever was similar in many respects to rat bite fever of bacterial etiology It was characterized by an *incubation period* of one to three days and an *abrupt onset* with *headache chills vomiting* and *fever* After a few days a *rash* appeared which was blotchy maculopapular and dull red in color Moderate *leukocytosis* was present *Agglutinins* for the specific organism developed in the patient s sera and it seems most likely that this was the same disease as rat bite fever due to *Streptobacillus moniliformis* but modified by a different method of transmission

DIAGNOSIS

The only certain differentiation of the two forms of rat bite fever is by laboratory methods *Streptobacillus moniliformis* may be cultured from blood abscesses or joint fluid It requires special media and special technic It is also possible to make the diagnosis by the demonstration of specific agglutinins for the organism in the patient s serum

TREATMENT

Haverhill fever in the manner of the treponematoses is best treated with penicillin (p 106) Injections of 40 000 units in solution may be made every three hours for seven to ten days or 300 000 units in oil wax may be deposited twice daily for a like period

ANTI INFECTIVE AND ANTIBIOTIC AGENTS

Whereas sulfonamides are without value in the treatment of Rocky Mountain spotted fever both penicillin and para aminobenzoic acid (p 186) have proven utility The latter as in typhus (p 374) is the antibiotic of choice An initial oral dose of 4 0 to 8 0 gm (60 to 120 grains) with bicarbonate of soda is followed at two hour intervals by maintenance doses of 2 0 gm (30 grains) until the patient has been afebrile for forty eight hours Supplemental penicillin therapy may be considered in severe resistant or protracted infections (p 104)

VACCINE

A vaccine has been used for *active immunization* particularly in the western states The vaccine is a phenolized suspension made by grinding up infected ticks It is believed by the United States Public Health Service that this vaccine has prevented the disease in many cases or has made subsequent attacks less severe It is recommended that persons living in endemic areas and frequently exposed to ticks be immunized each year The dose is 1 cc subcutaneously for children and 2 cc for adults Two or three doses are given at weekly intervals

SERUM

A specific anti Rocky Mountain spotted fever rabbit serum is available for active treatment If given within twenty four hours after onset it suppresses the disease given after forty eight to seventy two hours it modifies the course favorably and has reduced the case fatality from 18 8 per cent to 3 8 per cent

ence of living cells and prefer to grow intracellularly resembling in this characteristic the filtrable viruses

Because rickettsiae cannot be grown in culture media apart from living tissue knowledge of their physiology and their chemical structure is

TABLE 26 —CLASSIFICATION OF RICKETTSIAL DISEASES (AFTER FELIX)

Disease	Main Foci	Principal Vector	Specific Antigen	Reservoir
Human Louse Borne Typhus				
Epidemic Typhus	Eastern Europe Chile Basutoland North Africa Union of South Africa	*P corporis*	OX–19	Man
Brill Disease	New York Boston	*P corporis*	OX–19	
Trench Fever	Central Europe	*P corporis*	OX–19	
Flea Borne Typhus				
Endemic Typhus	Southern United States	*X cheopis*	OX 19	Rat
Tarbadillo	Mexico Guatemala	*P corporis* o *X cheopis*	OX–19	
Manchurian Fever	Manchuria	*X cheopis*	OX 19	
Toulon Ship Typhus	Toulon Brest	*X cheopis*	OX–19	
Endemic Australian Typhus (Hones Disease)	Southern and Western Australia	*X cheopis*	OX–19	
Indian Typhus	Madras Southern India	*X cheopis*	OX–19	
Shop Typhus of Malaya	Cochin-china Malaya Java Sumatra	*X cheopis*	OX 19	
Mite Borne Typhus				
Rural Typhus of Malay	Malaya Sumatra	*T deliensis*	OX–K	Field Mice
Mite Fever of Sumatra	Sumatra	*T deliensis*	OX–K	
Japanese River Fever	Japan Formosa Malaya Sumatra New Guinea	*T akamushi*	OX–K	
Indian Typhus (NK Type)	Northeastern India	*T akamushi*	OX–K	
Queensland Coastal Fever	Northeast coast of Queensland	*L australiensis*	OX–K	
Tick Borne Typhus				
Boutonneuse Fever	Mediterranean Basin	*R sanguineus*	OX–19	Wild rodents
Kenya Tick Bite Fever	Kenya	*R sanguineus*	OX–K	
South African Tick Fever	Transvaal Southern Rhodesia	*A hebraeum*	OX–K	
Rocky Mountain Spotted Fever	Montana Idaho New York Maryland	*D andersoni* *D variabilis*	OX–19	
Sao Paulo Typhus	Sao Paulo Brazil	*A cajennense*	OX–19	
Minas Geraes Typhus	Brazil	*A cajennense*	OX–19	
Q Fever	Montana Idaho Maryland Australia	*D andersoni* *H humerosa*		

scanty As is also true of the filtrable viruses the rickettsiae are recognized and differentiated chiefly by the pathological reactions which they produce in man and in experimental animals and by the specificity of the immune responses resulting from infection

including bundle branch block delayed AV conduction time or slurring of the QRS waves

In fulminating cases there may be cyanosis severe dyspnea profound tachycardia auricular fibrillation gallop rhythm pulsus alternans or cardiac dilatation Difficulty in hearing is encountered in 34 per cent and abdominal distention in 60 per cent

Diagnosis —The diagnosis of tsutsugamushi fever rests on the demonstration of specific agglutinins for OX–K See *Differential Diagnosis of Eruptive Fevers* (pp 192 194)

Treatment —Tsutsugamushi fever may be prevented in large part by the use of long trousers and sleeves and tight collars Clothing should be impregnated with dimethylphthalate and dibutylphthalate for insect repellence Additional preventive therapy is afforded by vaccine injection

As in the case of other rickettsial infections the oral use of para aminobenzoic acid (p 136) has proven curative value After an initial



Fig 59 —Primary lesion of scrub typhus (tsutsugamushi fever)

dose of 4 0 to 8 0 gm (60 to 120 grains) maintenance doses of 2 0 gm (30 grains) are given with bicarbonate of soda until the patient has been afebrile for forty eight hours Sulfonamides and digitalis are ineffective Penicillin may be reserved for overwhelming resistant or protracted infections in order to supplement the more potent agency

Convalescence may be tedious and prolonged with persistent asthenia for many months

Q FEVER (NINE-MILE FEVER)

Q fever a mild illness characterized by fever and respiratory symptoms resembles influenza The disease has been recognized in Australia for some time and in 1937 the causative agent was found to be a rickettsia The

* Courtesy U S A Typhus Commission

CHAPTER 16

RICKETTSIAL INFECTIONS: TYPHUS FEVER AND ROCKY MOUNTAIN SPOTTED FEVER

Typhus Fever
  Endemic (*Rickettsia prowazeki*)
  Murine (*Rickettsia mooseri*)
Rocky Mountain Spotted Fever (*Rickettsia rickettsi*)

TYPHUS FEVER

THERE are two principal varieties of typhus fever *European* or *epidemic typhus* is louse borne and *American* or *endemic typhus* is transmitted to man by the rat flea Both are rickettsial diseases and while clinically similar in general they exhibit certain differences in severity in their pathological effects on animals and in epidemiology Antigenically the infectious agents are similar but are not identical

Brill s disease is regarded as a variety of European typhus *Sao Paulo typhus* which occurs in Brazil more properly belongs with the spotted fever group of diseases (p 376)

EUROPEAN OR EPIDEMIC TYPHUS

Epidemic typhus fever is an acute infectious disease caused by *Rickettsia prowazeki* and transmitted by the *human body louse* Clinically it is characterized by abrupt onset stupor a sustained fever falling by crisis and a generalized eruption

GEOGRAPHICAL DISTRIBUTION AND INCIDENCE

For many centuries Europe has been a principal center of typhus The two major foci are in *Poland* and the *U S S R* During World War I as in all previous European wars typhus was epidemic and in Serbia a very malignant form of the disease occurred in 1915

In the U S S R from 1919 to 1922 it is estimated that more than 5 000 000 cases of typhus occurred Since that time vigorous preventive methods especially aimed at the destruction of body lice have greatly reduced the prevalence of the disease but it is far from eradicated Whenever war and famine force people into close overcrowded quarters without the opportunity for personal hygiene typhus can be expected European typhus was common along the Eastern seaboard of the United States until some time after the Civil War Today European typhus does not exist in this country but *murine typhus* (p 375) is prevalent especially in the southern states

Etiology—As a result of the work of Ricketts Rocha Lima, Wolbach and others it is now definitely established that European typhus is caused by *Rickettsia prowazeki* The organism is found intracellularly in the vascular endothelium of fatal human cases and in the gut of lice after they have fed on human victims of the disease

Transmission—Typhus is transmitted by the *body louse* (*Pediculus humanus var corporis*) The rickettsiae grow readily in the body of the louse and are excreted in the feces

appears The regional lymph nodes become enlarged and the rash unlike that of typhus fever covers the entire body including the face palms and soles The pulse is slow in proportion to the fever the spleen is not enlarged nervous symptoms are not prominent the temperature returns to normal on the twelfth to fifteenth day Death is rare and complications are uncommon Para aminobenzoic acid therapy (p 136) is indicated

COLORADO TICK FEVER

Colorado tick fever is also known as tick toxemia mountain fever and American mountain fever It may be a distinct clinical entity its distribution is similar to the western type of spotted fever The causative agent has not yet been identified but the vector is the *wood tick*

Clinically Colorado tick fever resembles Rocky Mountain spotted fever The onset is sudden the height of temperature is usually reached in 24 hours Ordinarily there are two febrile periods each one from two to four days duration with a remission period of seven days There is no eruption but at the site of the tick bite an indolent ulcer may appear

Blood serum from infected cases does not agglutinate any of the strains of the proteus animal inoculation is ineffective

Para aminobenzoic acid therapy (p 136) is indicated

VERRUGA PERUANA (OROYA FEVER CARRION S DISEASE BARTONELLOSIS)

Oroya fever occurs only in certain endemic areas in Peru and has been present there from the beginning of historical times Severe epidemics have occurred and it is said that one quarter of the troops of Francisco Pizarro who invaded Peru in the early part of the sixteenth century perished from this disease

It was long recognized that there was a close relationship between a severe often fatal febrile anemia (*Oroya fever*) and a cutaneous verrucous eruption (*verruga peruana*) In 1885 Daniel Carrion inoculated his skin with material obtained from the nodules of verruga peruana and subsequently died of Oroya fever In honor of this medical martyr the acute stage of the disease is often called *Carrion s disease*

Etiology—In 1905 Barton described numerous bacillary like organisms in the red blood cells of patients with Oroya fever This was confirmed by many other workers and the organisms were subsequently named *Bartonella bacilliformis* Noguchi succeeded in cultivating the organisms on his leptospira medium The verruga type of disease was reproduced in monkeys but the Oroya stage of the disease was never successfully reproduced although the organisms were occasionally seen in red blood cells Recently they have been grown in tissue culture and in the developing chick embryo In stained blood smears *Bartonella bacilliformis* appears as tiny rod shaped or rounded organisms from 1 to 2 μ in length It is also found in endothelial cells especially in the lymph nodes spleen liver and intestines in fatal human infections

The classification of these organisms is still uncertain They were described and named before the rickettsiae were discovered and they have much in common with these organisms Morphologically they are similar and are both found intracellularly in human tissues However Bartonellae are present within red blood corpuscles whereas Rickettsiae are not. Both are retained by most porcelain filters Rickettsiae cannot be grown apart from living cells and Bartonella has been grown in artificial medium In general the two organisms are considered closely similar occupying a position midway between bacteria and filtrable viruses

Epidemiology—Oroya fever is confined almost entirely to certain areas of Peru although cases have been reported from Colombia to Ecuador In endemic regions almost all inhabi

fever rises rapidly after onset and by the third or fourth day reaches 104° to 105° F This temperature is maintained with very little diurnal variation until the twelfth to fourteenth day when in favorable cases it falls rapidly to normal

The characteristic eruption appears on the fourth day of illness as *pink macules* 2 to 6 mm in diameter over the axillae and loins These spread rapidly over the abdomen chest and back but the face is uninvolved The lesions at first disappear on pressure but later become somewhat hemorrhagic The rash persists until the critical fall in temperature when it rapidly fades In color the eruption is at first pink then bright red and later purple It rarely involves palms and soles in contradistinction to the rash of spotted fever See *Differential Diagnosis of Eruptive Fevers* (pp 172 174)

Cough usually develops at the time of the appearance of the rash It is due to *bronchitis* but *bronchopneumonia* may occur as a complication *Dryness of the mouth* is very prominent and bothersome and probably accounts for the tendency to develop *parotitis* *Nervous symptoms* are outstanding features of the disease The *severe headache* at the onset of symptoms improves in a few days but is succeeded by a dull stuporous state In the second week of the disease the stupor may give way to *delirium* and *excitement* requiring forceful restraint In fatal cases *coma* precedes *death*

Profound circulatory depression with low blood pressure rapid weak pulse and feeble heart sounds occurs during the course of the disease These cardiovascular disturbances contribute to the necrosis and gangrene which sometimes occur over pressure points and in the extremities Pathological involvement of the arterioles of the skin and degenerative changes in the myocardium account for the circulatory depression

COURSE AND COMPLICATIONS

After twelve to fourteen days the fever falls rapidly to normal the mental confusion clears and the patient feels greatly improved The defervescence of typhus is comparable to a crisis in lobar pneumonia Convalescence is usually complete in a few weeks

Complications include *bronchopneumonia otitis media parotitis* and *gangrene* of the skin or soft tissues *Encephalitis* sometimes occurs and is marked by a progressive coma leading to death At autopsy there are numerous vascular lesions in the brain of the type already described

BRILL S DISEASE

In 1898 Brill first observed cases of an acute febrile illness in New York City which resembled classical typhus fever They were milder than the European disease and differed also in certain important epidemiological features Thus the cases occurred sporadically and did not have the typical seasonal distribution of European typhus There was no evidence of louse transmission nor did the disease ever occur epidemically

The present concept of this disease follows the work of Zinsser He showed that the cases occurred along the eastern seaboard of the United States chiefly in Boston and New York An investigation of the record

covery from the acute stage occurs it is generally followed by the development of the cutaneous lesions of verruga peruana

VERRUGA PERUANA

The cutaneous phase of Oroya fever lasts two or three months and is characterized by a successive eruption of crops of skin lesions which may be pea sized miliary or larger nodules These lesions are somewhat wart like and have a tendency to bleed and ulcerate The miliary lesions may involve mucous membranes At the onset there are generally fever and arthralgia which tend to disappear as the eruption develops The verruga stage of the disease is rarely fatal unless complicated by other infections

DIAGNOSIS

The diagnosis of Oroya fever is easily made in severe cases from the clinical appearance the hematological findings and the demonstration of *Bartonella bacilliformis* in red blood cells stained by Wright s or Romanowsky s method The organisms have a bluish color and contain red chromatin at one extremity

TREATMENT

The usual forms of therapy for anemia are ineffective as would be expected Transfusion should be tried and a course of penicillin is distinctly indicated in probatory fashion as a measure of desperation particularly in Carrion fever A specific serum has been prepared and its use is advocated Para aminobenzoic acid may be tried as in typhus fever (p 374)

KEW GARDENS SPOTTED FEVER (RICKETTSIALPOX)

Kew Gardens spotted fever appears to be a hitherto undescribed rickettsial infection It is mild in intensity and may afflict both infants and adults

The onset is indefinite until the discovery of an area of erythema resembling an insect bite and regional adenopathy The initial lesion usually appears around the shoulders or in the axilla Some time within the next eight days the patient notes malaise chilliness occipital headache and fever Over chest abdomen and upper extremities there then appears a punctate macular rash which does not fade on pressure At first the eruption is sparse but new spots appear for several days

After another week of fever the temperature diminishes and the eruption fades but the initial lesion and the regional adenopathy persist Neither generalized lymphadenopathy nor splenomegaly is observed Except for slight leukopenia laboratory examinations are not informative Specific agglutination and complement fixation tests for the known allied diseases are negative suggesting that Kew Gardens fever is a distinct and hitherto unrecognized entity

By analogy treatment with para aminobenzoic acid (p 136) is indicated as in typhus (p 374)

Friedlander bacillus and the type II pneumococcus have similar capsular polysaccharides and both react with the same antiserum

The proteus culture recommended by Weil and Felix for agglutination tests is called the X 19 *strain* It dissociates into H (motile) and O (non motile) forms It is the latter *OX 19* which is used for rickettsial agglu tination More recently other strains of proteus bacillus OX 2 and OX K have been added The test is a simple *macroscopic agglutination reaction* using standard amounts of the *various proteus strains as antigens* and serial dilutions of the patient s serum It has been found that the various groups of rickettsial diseases react differently with the several strains of proteus and this fact is of some diagnostic importance Table 27 showing the degree of reactivity of different disease groups with the strains of proteus is taken from Felix s data

TABLE 27—REACTIVITY OF DISEASE GROUPS WITH PROTEUS BACILLUS

	Typhus Group	Spotted Fever Group	Tsutsugamushi
B proteus OX 19	+ + +	+	— —
B proteus OX 2	+	+	— —
B proteus OX K	— —	+	+ + +

In epidemic typhus agglutinins for OX 19 are demonstrable by the end of the first week of the disease and the titer rises to its highest point at about the time of crisis after which it falls steadily but may still be demon strable for months Titers of less than 1 80 have no significance The titer may rise to 1 2000 or more but as is true for most agglutination reactions the trend of the titer is often of greater importance in diagnosis than its absolute height

Animal Tests—*Guinea pigs* are susceptible to typhus and spotted fever infections when injected intraperitoneally with 5 cc or more of the pa tient s blood The blood must be taken within four days or six days after clinical onset European typhus produces fever and eventual death of the animal but with no particular involvement of the scrotum On the other hand endemic typhus and spotted fever cause swelling and inflammation of the scrotum of guinea pigs A further differentiation of epidemic and endemic typhus is the response of *rats* to infection European typhus pro duces an inapparent infection of rats whereas endemic typhus produces a scrotal reaction (Fig 57)

Of more importance than the specific type of animal pathology are the results of *cross protection tests* in animals using the patient s and known rickettsiae or the unknown rickettsia with known [illegible]

Complement Fixation Tests—The cultivation of rickettsiae in [illegible] tures in the membranes of developing chick embryos and as suspensions of infected rat lungs has permitted the preparation [illegible] centrated and potent rickettsial antigens which can be used with serum in complement fixation tests These tests are relatively [illegible] the various rickettsial infections in the typhus and spotted fever as well as in Q fever Complement fixing antibodies develop in the [illegible] of typhus and spotted fever and persist for periods of many m[illegible] after The method is one which can easily be adapted for routine

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Of more importance than the specific type of animal pathology are the results of *cross protection tests* in animals using the patient s serum and known rickettsiae or the unknown rickettsia with known specific sera

Complement Fixation Tests—The cultivation of rickettsiae in tissue cultures in the membranes of developing chick embryos and as ground up suspensions of infected rat lungs has permitted the preparation of concentrated and potent rickettsial antigens which can be used with patient s serum in complement fixation tests These tests are relatively specific for the various rickettsial infections in the typhus and spotted fever groups as well as in Q fever Complement fixing antibodies develop in the course of typhus and spotted fever and persist for periods of many months thereafter The method is one which can easily be adapted for routine laboratory

stances An organism which lacks these metabolic enzymes and gets its food already digested might be of smaller size since there are fewer functions to be executed by the cell itself Carrying this hypothesis to its logical conclusion it is conceivable that viruses represent a stage of such complete parasitism that a great many, perhaps the majority of their functions are accomplished by the host or parasitized cell in which they live Stripped thus of all but a minimum of enzyme systems the virus is able to carry on vital functions and yet exist in a size not much larger than that of many protein molecules

Inclusion Bodies —One of the characteristic features of virus disease is the presence of inclusion bodies in infected cells of the host They may be intranuclear or within the cytoplasm they may take acid or basic stains



Fig 61 —Electron microscope pictures of viruses (× 20 600)

and appear homogeneous or contain numerous granules and other structures The nature of inclusion bodies has long been obscure At one time they were regarded as a stage in the elaborate life cycle of protozoa Others have regarded them as cellular reactions to damage by the virus Today there is clear evidence that many of them represent actual colonies of virus

Cultivation —With few minor exceptions viruses cannot be cultivated except in the presence of living tissue they may be grown in susceptible animals or in tissue cultures The majority of viruses pathogenic for man can be cultivated on the chorio allantoic membranes or in the yolk sac of developing chick embryo The technic of inoculation is not difficult A window is cut in the shell of a fertilized hen s egg and the infective material placed on the membranes of the developing embryo The window

* Courtesy of R C A., Camden N J

After preparation it may be sprinkled on clothing where it retains its insecticidal power through eight washings and will keep flies away for three months

ACTIVE IMMUNIZATION

Early attempts at vaccination employed suspensions of infected animal tissue containing living rickettsiae There is evidence that immunization with such material may be effective but the danger of using living organ isms has prevented the general use of this procedure The preparation of antigens of killed rickettsiae was hindered by the difficulty of preparing large quantities of the organisms Weigl developed an ingenious method of inoculating lice through the rectum In nine to twelve days the louse died and its intestinal wall was filled with rickettsiae Phenolized suspen sions of this material were used for producing active immunity in man but obviously this method could not be applied to large scale production Zinsser found that large amounts of endemic or murine typhus rickettsiae could be obtained from the peritoneal cavity of rats whose resistance was reduced by heavy doses of roentgen ray This material when killed ap peared to be useful in artificial immunization against endemic typhus but did not appear to give full protection against epidemic (European) typhus

Most recently it has been found that the organism multiplies enor mously when inoculated into the yolk sac of developing eggs and it is now possible to produce *rickettsia vaccine* in large quantities for *active im munization*

Three subcutaneous injections of 1 cc each are given at seven to ten day intervals The immunity persists for only six to eight months and in consequence booster doses of 1 cc are required every six months while danger exists The vaccine does not protect against flea borne typhus nor other rickettsial diseases Reactions are relatively slight and consist almost exclusively of local discomfort Because of the efficacy of D D T powder it has been impossible to evaluate with accuracy the preventive value of typhus vaccine but it may be stated with certainty that the combination of the insecticide and the immunological agent accomplishes maximum pro tection

ENDEMIC TYPHUS IN THE UNITED STATES (MURINE TYPHUS AMERICAN TYPHUS)

Endemic or murine typhus fever is widespread and of increasing impor tance in the United States The disease is mostly sporadic occurs more often in males and is considerably milder than classical typhus Many of the cases appear in food handlers and warehousemen Rats are the infec tious reservoirs and the disease is transmitted to man by rat fleas

Etiology—The rickettsia of endemic typhus is closely related to that of epidemic or European typhus as shown by partial but not complete cross-protection in animals

Geographic Distribution and Incidence—American or murine typhus is most common in the southern states The chief endemic foci are in *Georgia Alabama* and *Texas* In the country as a whole 196 cases were recognized in 19 8 332 in 1931 and more than 3000 in 1940 Whether the disease is really increasing in prevalence or is being more generally diag nosed is not clear

Transmission—Typhus is endemic in *rats* It is transmitted from rat to rat by the *rat louse* and the *rat flea* The rat louse does not bite man but the rat flea does Infection in man probably occurs as the result of *scratching flea bites* on which flea feces have been introduced There is also some evidence that man may be infected by *ingesting food con*

In the case of smallpox nature supplied the method and the keen observation of Edward Jenner applied it to human use For rabies Pasteur developed a method of *attenuating virus* by animal passage and drying At the present time active immunization can be carried out for *yellow fever equine encephalitis smallpox rabies* and possibly *influenza* The most recent technic for immunization is attenuation by exposure to ultra violet rays and this procedure holds promise in the prevention of polio myelitis and influenza

Passive immunity or modification of the disease can be obtained by the use of convalescent serum in the case of *measles chicken pox* and *mumps* and experimentally in *equine encephalomeningitis* Convalescent serums in the active treatment of virus diseases are of doubtful value and serotherapy in general is valueless

in Maryland Virginia and North Carolina At present it is recognized that spotted fever and endemic typhus are the two important rickettsial diseases of the United States

Etiology—H T Ricketts after whom rickettsiae are named did much of the pioneer work on the transmission of spotted fever The rickettsiae of spotted fever are found in infected ticks and in the tissues of patients at autopsy The susceptibility of guinea pigs to the infection and the characteristic growth of the organism in the cells of tissue cultures have been described in the previous section

Transmission—The division of the disease into eastern and western types has no particular justification since the rickettsiae are immunologically identical The *wood tick* (*Dermacentor andersoni*) is the vector of western spotted fever and the *dog tick* (*Dermacentor variabilis*) in the eastern variety The organism is transmitted by the adult tick to its eggs so that the rickettsial infection is hereditary in these insects Man is accidentally infected by the bite of ticks Contact infection from diseased individuals does not occur The human disease because of the mode of transmission remains sporadic

The disease occurs during the seasonal prevalence of ticks i e April May or June for the western type and June July or August for the eastern type The greatest number of cases occur among those whose occupations take them into tick infested areas Ranchmen and shepherds are most often affected by the western type of spotted fever On the other hand the eastern type occurs among all age groups and in both sexes equally This is probably due to the fact that vacationers are more likely to come in contact with dog ticks

Pathology—The microscopic lesions of spotted fever are similar to those of typhus and occur in the blood vessels of the skin subcutaneous tissues muscles testes and brain The individual lesion consists of a proliferation of the vascular endothelium followed by necrosis with thrombus formation Rickettsiae are found in the vascular endothelium and in the smooth muscle cells of the vessel walls

Synonym —Rocky Mountain spotted fever is probably identical with Sao Paulo fever tick fever and pinta fever

Clinical Manifestations

The great majority of cases pursue a typical course The *incubation period* varies from three to fourteen days There may be a vague prodromal period of one or two days but the *onset* is generally abrupt and marked by *headache pains in the back extremities joints and muscles* See *Differential Diagnosis of Commoner Febrile Skeletal Disorders* (p 192)

The temperature rises rapidly and by the second or third day reaches a plateau of 103 to 105 F in severe cases In milder instances the temperature rise is more gradual and the maximum elevation may not be recorded before the end of the first week of illness The febrile period lasts two or three weeks Maximal elevations of temperature persist for about two weeks with but little daily variation and then the fever falls slowly to normal by the end of the third week The rapid crisis of epidemic typhus is not seen in spotted fever In the most severe examples of the disease the temperature may drop to normal or subnormal levels only to rise terminally In fatal cases death is most likely to occur during the second or third week of the disease Mild ambulatory attacks with little fever also occur and the rash may be scanty or extensive At the other extreme are fulminating cases with death in three or four days

The Eruption —The rash is the most characteristic clinical and diagnostic feature of spotted fever It appears on the second to the fourth day as a *macular* or *maculopapular eruption* of a pale to bright rose color later becoming distinctly *petechial* in character The eruption develops in characteristic manner It appears first on the wrists or ankles and spreads centripetally over the extremities scalp chest and abdomen It is always most

den fall in temperature of as much as ten degrees in a week seems to precipitate an increase in the incidence of the upper respiratory infection It is commonly believed by the laity that draughts and chilling are provocative factors in the production of colds While it is conceivable that these conditions may have precipitating importance they certainly have no direct etiological implications The mechanism by which these phenomena become important is probably through the production of a *reflex ischemia* of the mucous membrane with a resultant lowering of local resistance to invasion by the infectious agent

The *resistance* of the virus of the common cold is incredibly great. Thus ultraviolet radiation of the air of classrooms and hospital wards is capable of preventing the air borne transmission of other virus diseases such as measles chickenpox and influenza whereas the incidence of the common cold is completely unaffected In massive dose chemotherapy of syphilis where arsenic concentrations were obtained of sufficient strength to kill the spirochete that causes the luetic infection the common cold was observed to pursue its normal course without modification

Lay opinion to the contrary smoking sleeping eight hours a night taking cold baths, breathing exercises through the mouth the wearing of rubbers and the use of umbrellas seemingly have nothing to do with the etiology of the complaint

Clinical Manifestations

See *Rhinitis* under *Respiratory Infections* (p 2114)

Prevention

The prophylaxis of the common cold has been summarized by the statement that no one has any right to proclaim on scientific grounds that there is any means of warding off a cold' The single modification of this broad statement might be to the effect that the common cold is preventable by avoidance of carriers and individuals affected with the specific virus

Despite this enunciation of therapeutic nihilism the American public expends annually millions of dollars and countless hours of conversation upon preventive treatment Some of these prophylactic modalities are specific others are aimed at principles of hygiene Penicillin aerosolization (p 2041) or administration of *sulfadiazine* in 1 gm (15 grain) doses three times daily may reduce the incidence of secondary coccal complications

Bacterial Vaccines

Commercial and autogenous bacterial vaccines are widely used for the prevention of the common cold Ordinarily these preparations contain pneumococci Types I and III *Streptococcus viridans* Friedlander bacillus *Streptococcus haemolyticus* the *bacillus of influenza* *staphylococcus* and *Micrococcus catarrhalis* Suspensions of bacterial bodies and filtrates are in commonest use

Of all these vaccines one statement stands indisputable and that is the observation that no one of these preparations contains the cause of the common cold Under these conditions the best that proponents for their use can maintain is that they raise the resistance of the host to the bacterial infections that are so commonly associated with the cold syndrome Certainly no serious investigator can conscientiously believe or state that it is possible to produce a specific active immunization with any of these preparations These scientific observations are well borne out by practical experience Whether the cold vaccine is given subcutaneously or orally in capsules controlled studies reveal little or no difference in the incidence

fatal complication A *bleeding tendency* is evident in most patients and in seriously ill patients there are often epistaxis hematemesis melena and hemorrhage in the skin *Gangrene* of the scrotum fingers toes ear lobes vulva soft palate and tonsils occurs in the terminal stages of fatal illnesses In those who survive convalescence is slow and extends over many weeks

Diagnosis

Typhoid fever measles scarlet fever meningococcemia and smallpox may be confused with spotted fever but clinical and laboratory diagnostic criteria clarify most conditions The differentiation of spotted fever from *endemic typhus* is difficult especially since both diseases occur in the same geographical areas A *history of a tick bite* is good evidence in favor of spotted fever and this disease is more likely to occur among rural residents The rash of spotted fever is heavier and more generalized and tends to involve the palms and soles The eruption appears first on the extremities and later on the face and trunk while in typhus the eruption begins on the body and spreads centrifugally to the extremities See *Differential Diagnosis of Eruptive Fevers* (pp 192 194)

Since mild and atypical attacks are common in both diseases additional help must be sought in the laboratory Blood from the patient may be taken in the first six days of the disease and inoculated into guinea pigs The character of the infection in this animal has been described (p 373) Cross protection and neutralization tests can be done and these will generally differentiate the typhus group of organisms from the spotted fever group The importance of the *Weil Felix reaction* has already been discussed (p 372) *Complement fixation tests* generally become positive by the end of the first week and persist over a period of several months

Prognosis

Case fatality rates vary widely In Montana the case fatality was formerly reported at 70 to 90 per cent but more recently it has been about 15 per cent In the eastern states the case fatality has been about 18 per cent for several years There has existed a belief that the western type of disease had a far higher mortality than the eastern type An analysis of the age distribution of cases however showed that more older persons contracted the western type and more children the eastern type When the age factor is adjusted the case fatality rate in the two forms of the disease becomes equal As is the case with endemic typhus the disease is least fatal in children and the mortality increases with advancing age

Treatment

Measures to eradicate ticks have been undertaken in the endemic areas of Montana and Idaho but they are difficult to carry out and not especially practical Obviously avoidance of areas known to be infested with ticks is the best way to avoid the disease Those who must enter such areas should dress so as to prevent tick bites The tick feeds for a number of hours on the human skin hence infection may be prevented if the insect is quickly removed and the wound is cauterized with fuming nitric acid

Other drug remedies popularly advised for cold prevention include saline purges alkalinization with bicarbonate of soda catharsis with diuretics (the cold laxatives'), nasal sprays nasal vapors gargles lozenges cough drops the inhalation of chlorine vapor a slug of whiskey the mustard foot bath the mustard chest plaster tea with rum a Turkish bath a colon irrigation or a massage to mention only a few of the recurrently advocated miracles The multiplicity of the prescriptions indicates that no one has significant value

There is considerable difference of opinion as to the efficacy of the anti infective agents in the prevention of the common cold Certainly *penicillin* has no specific value whether locally or systemically introduced An antibiotic substance *patulin* (p 103) has been proved of little value despite enthusiastic introduction

The majority of investigators agree that the *sulfonamides* do not shorten or alter the course of the uncomplicated cold Other equally careful observers however are firm in the belief that as small a dose as 1 gm (15 grains) of *sulfadiazine* given three times daily reduces the incidence of infection the duration of the disease and the numbers of the complications

Active Treatment

The active treatment of the common cold is almost as discouraging as prevention In addition to the preparations mentioned in the discussion of prevention there is a multiplicity of other *cold cures* both ethical and unethical At best a few of these preparations afford symptomatic relief The rest are useless or even harmful and illustrate the exploitation of a gullible public

The popular remedies which are widely advertised constitute a hoax They include *inhalants* which are merely an oily base like petrolatum with a volatile oil such as eucalyptus menthol or thymol *rubs* which differ from the inhalants only in that they have a sticky base and perhaps a counter irritant such as mustard *nose drops* identical with the recognized vaso constrictors and containing for sales purposes a coloring agent and a volatile oil *cough drops* *cough syrups* and *throat lozenges* and *capsules* or *cachets* containing the ordinary coal tar drugs embellished by the sales talk of the advertising copywriter

General Principles

It is our practice to tell patients that the common cold is a self limited disease and that we have no method of aborting or curing the affliction We quote the axiom that the common cold lasts two weeks if treated and a fortnight if untreated We do not pretend to be able to contribute anything significant other than symptomatic relief and we strive to prevent our patients from exposing themselves to charlatanism within and without the medical profession We oppose instrumentation of the respiratory passages during the acute and catarrhal phases We have not the slightest patience with those who paint the throat with silver proteinate or pack the nostrils with tampons containing similar preparations

The patient with the common cold should *remain at home* and preferably *in bed* This will not only accomplish a reduction in the duration of the disease and the incidence of complications but it also serves to protect

CHAPTER 17

RICKETTSIAL INFECTIONS CONCLUDED

Tsutsugamushi Disease (*Rickettsia orientalis*)
Q Fever (*Rickettsia burneti*)
Trench Fever
Bullis Fever
Boutonneuse Fever (*Rickettsia conori*)
Colorado Tick Fever
Verruga Peruana (*Bartonella bacilliformis*)
Kew Gardens Spotted Fever

TSUTSUGAMUSHI FEVER

Tsutsugamushi fever (scrub typhus mite bite fever Kedani Malaya typhus exanthematous glandular fever tropical typhus) is endemic in Sumatra New Guinea Java Borneo Formosa Japan Australia and the Federated Malay States

Etiology—Scrub typhus is acquired on exposure to certain types of vegetation in circumscribed areas of untilled open country and especially land that has been cleared of jungle and has subsequently been overrun by weeds and scrub The etiologic agent is *R ckettsia orientalis* the vector is the *mite* genus Trombicula or chigger Field mice rats bandicoots and other small animals which harbor the larval mite act as infectious reservoirs of the disease

Pathology—The primary pathologic changes include vasculitis and perivasculitis with slight tendency toward thrombus formation The perivascular extension of the infection involves the parenchyma of various organs these changes are reflected in the clinical picture The histopathologic changes are most marked in heart lungs and brain

Clinical Manifestations—The usual incubation period probably varies from four to twenty one days The patient is usually bitten while logging Vague complaints of malaise chilliness vertigo headache and insomnia may precede the onset of fever Physical examination often reveals an eschar at the site of the mite bite which is usually *scrotal inguinal* or on the *ankle* The *primary lesion* is an ulcer with a black central necrotic area surrounded by an indurated red areola Extensive *adenopathy* is common the spleen is frequently but not invariably palpable

By the fifth to the eighth day of the disease the majority of patients have a *maculopapular erythematous rash* involving as a rule the lateral or anterior thorax or abdomen with the extremities least affected The rash lasts about eight to twelve days *Epistaxis* is common and more than half the patients develop a *pneumonitis* See *Differential Diagnosis of the Commoner Febrile Intrathoracic Disorders* (p 404)

The febrile stage may persist up to four weeks the average duration being seventeen days The cardiovascular system is profoundly affected by the disease The pulse rate is usually increased but does not exceed 120 beats per minute when it becomes more rapid it signifies impending myocardial failure Objective findings include apical systolic murmurs premature contractions and inconstant and infrequent cardiographic changes

icines cough syrups narcotics and opiates partly because they are essentially valueless and partly because they interfere with the cough reflex and hence favor the retention of secretion

ANTI INFECTIVE AGENTS

As in the instance of the prevention of the common cold there are conflicting opinions regarding the value of the anti infective agents in the treatment of this common ailment Nebulization and aerosolization (p 2041) with penicillin solutions (1 cc equals 10 000 to 100 000 units) reduces discomforts and complications through effects on secondary coccal invaders rather than from direct suppression of the offending virus

We are among those who have no enthusiasm for the use of *sulfonamides* in the treatment of the common cold We are definitely opposed to the topical use of the remedy in nose drops since local activity of the *remedy is negligible in the presence of pus and dead bacteria* Furthermore the initiation of this form of therapy may produce toxicologic manifestations organisms may be rendered sulfonamide resistant and the patient may be made hypersensitive so that these potent remedies cannot be given at a future time when there is urgent need

Our present practice in the use of sulfonamides may be summarized by the following (1) We oppose the routine use of sulfonamide drugs in the prevention of the common cold (2) we oppose the use of sulfonamide therapy in the active treatment of the common cold (3) we advocate strongly the administration of the sulfonamides in the later stages of the common cold or upon the development of secondary bacterial infections particularly in the middle ear or the accessory nasal sinuses (4) we advocate the use of the sulfonamide drugs for the prevention and treatment of complications of the common cold in those with congestive heart failure rheumatic fever the allergies particularly bronchial asthma chronic pulmonary disease such as bronchiectasis pulmonary tuberculosis or empyema the cardiac invalid the pregnant and the woman who is recently postpartum the postoperative and the sufferer from chronic disease such as a severe diabetes or renal insufficiency

INFLUENZA (GRIPPE)

Influenza is an acute infectious disease of high communicability It is characterized by an abrupt onset a short course with systemic and respiratory symptoms and a tendency to bacterial complications especially pneumonia The disease occurs throughout the world It is seen annually in endemic form frequently in localized or large epidemics and at intervals of several decades in great pandemics

Etiology—During the pandemic of 1889–90 Pfeiffer isolated a *gram negative bacillus* from the throats of patients with influenza This organism was given the name of influenza bacillus (*Hemophilus influenzae*) or Pfeiffer s bacillus and was accepted as the cause of influenza It is now agreed that the organism is commonly found in the normal respiratory mucous membrane and is not the primary cause of influenza though it may and does produce other clinical diseases elsewhere described (p 285)

In 1931 Shope found that swine influenza a disease resembling human influenza was due to a *filtrable virus* A short time later (1933) ferrets were infected with the nasal washings of a patient with clinical influenza Upon recovery the animals were resistant to reinfec-

blood of patients was infectious for guinea pigs and from the spleens of the latter the organisms could be recovered It is thought that the natural reservoir of infection is the *bandicoot* and that *ticks* are the vectors by which man is infected In 1938 a similar rickettsia was found in wood ticks in Montana Infection in man produced *nine-mile fever* As a result of cross immunity experiments it was established that these two infections and the rickettsiae causing them are identical

In 1940 there occurred at the National Institute of Health in Washington a number of cases of *atypical pneumonitis* From several of these patients after inoculation of guinea pigs rickettsiae were recovered which were identical with those of Australian Q fever and the nine mile fever of Montana It thus became apparent that this rickettsia for which the name *Rickettsia burneti* has been adopted is one cause of atypical pneumonitis although other etiological agents also appear to have been recovered from patients with this disease (p 400)

Specific agglutinins and complement fixation antibodies have been detected in the serums of patients infected with *R burneti* but the Weil Felix reaction is negative The recent experiences with para aminobenzoic acid in typhus fever (p 374) justify a trial of the drug in the treatment of Q fever and Nine Mile Fever

TRENCH FEVER (WOLHYNIAN FIVE DAY MEUSE OR SHIN FEVER)

Trench fever is a disease which was first widely recognized as an entity during World War I At that time it was very prevalent among troops in the trenches While it had practically no mortality it accounted for one fifth of all cases of illness in the British army in France and other armies were equally affected It was shown that trench fever was transmitted by the human body louse The blood of patients was infectious and volunteers could be infected by the bite of the louse or by the injection of blood from a patient Although the disease was placed among the rickettsial infections there is no definite evidence that it is of rickettsial etiology Rickettsiae are sometimes seen in lice but apparently they are not regularly present The disease has not been transmitted to laboratory animals

Trench fever is characterized by *headache dizziness muscle pains backache a relapsing fever splenic enlargement* and a *papular eruption* Para aminobenzoic acid therapy (p 136) is indicated

BULLIS FEVER

A rickettsial fever has been described at Camp Bullis in Texas The disease consists of a short fever following an incubation period of nine to twelve days Relapses are observed and enlargements of the spleen and lymph nodes occur An infectious agent has been obtained from macerated ticks that produces the disease in guinea pigs Immunologically Bullis fever is differentiated from spotted fever and Q fever The principal *vector* is *Amblyomma americanum* Para aminobenzoic acid therapy (p 136) is indicated

BOUTONNEUSE FEVER

Boutonneuse fever is a non fatal tick borne disease of the Mediterranean Coast and the region of the Black Sea It appears in the middle or late summer and resembles typhus fever except that at the site of the tick bite one to three discrete painless ulcerated spots develop before the rash

cyanosis of the lips The eyes are glistening the conjunctivae are suffused and there may be a sticky exudate There is obstruction to nasal breathing At first the nasal mucosa is dry, but later a slight serous discharge is apparent The tongue is coated and the mucous membranes of the pharynx are red dry and glistening There may be some lymphoid hyperplasia but exudate is quite uncommon The pulse is full and bounding the rate being proportionate to the elevation of temperature

In two thirds of uncomplicated cases of influenza *abnormal physical signs in the chest* can be detected For the most part these consist of *rhonchi* and a *few coarse moist rales* at both bases Roentgenographic examination of the chest reveals no abnormalities but the physical signs together with the dry cough scanty white sputum and substernal soreness make it probable that tracheobronchitis is an essential feature of the disease In a smaller number of patients there are in addition to rhonchi *finer rales* and *abnormal breath sounds* Small areas of dullness and diminished breath sounds are detected These disappear after coughing suggesting that they are small areas of temporary *atelectasis* rather than true consolidation Such patients may be regarded as having an extension of the catarrhal inflammation down to and including the bronchioles

See *Differential Diagnosis of Commoner Febrile Intrathoracic Disorders* (p 404)

Diagnosis

The clinical diagnosis of influenza is unsatisfactory except in recognized epidemics The symptomatology may be extremely varied Mild attacks characterized by nasal obstruction and watery discharge with little or no constitutional symptoms are ordinarily called common cold When the attack is somewhat more severe with fever and malaise, it is commonly given the name *grippe* which from an etiological point of view means nothing since symptoms of grippe may be produced by cold virus influenza virus or bacterial infections of the upper respiratory tract Finally if the constitutional symptoms of headache malaise pain in the back and extremities and fever are marked the diagnosis of *influenza* is made

Influenza we would again emphasize is an epidemic disease As far as we are aware influenza virus has never been isolated from any sporadic or isolated case of respiratory disease Hence no matter how typical the clinical features may be the physician should hesitate to make a diagnosis of influenza except during an obvious epidemic of respiratory disease Parenthetically influenza virus has never been isolated from a patient with *intestinal flu* Although gastrointestinal symptoms may occur in the course of influenza they never constitute the primary or outstanding manifestation of the disease and are usually due to an overzealous use of cold laxative specifics

The various degrees of clinical severity of influenza probably are related to the immune state of the individual Volunteers in whom nasal washings containing virus were instilled developed mild moderate or severe symptoms Those who developed severe symptoms had no virus neutralizing antibodies in their serum previous to the inoculation while those who experienced mild symptoms had neutralizing antibodies beforehand

tants are infected generally in childhood Visitors to these regions invariably become infected unless they take precautions to prevent insect bites Immunity to both forms of the disease results from an attack of either form It is generally believed that insects particularly the *phlebotomus* or *sand fly* play an important role in transmission

Pathology—Patients dying of Oroya fever have a characteristic *waxy pallor* suggestive of pernicious anemia The *liver* and *spleen* are enlarged and may be infarcted The *lymph nodes* are swollen and the *heart muscle* is pale and flabby Microscopically the endothelial cells of the lymphatics of the spleen liver lymph nodes and kidneys are distended with *Bartonella bacilliformis* organisms which are also present in the red blood corpuscles

The cutaneous lesions of verruga peruana are highly vascular *granulomata* consisting of *newly formed blood vessels lying in edematous connective tissue* The causative organisms may be demonstrated in the vascular endothelial cells

Clinical Manifestations

The Carrion fever or generalized febrile state and the cutaneous variety of Oroya fever will be separately discussed

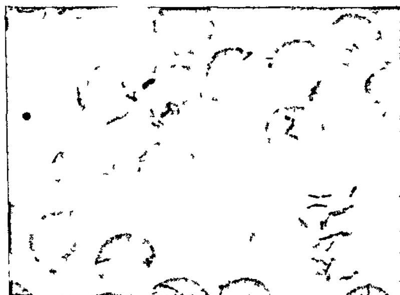


Fig 60—Bartonella bacilliformis in blood

CARRION FEVER

The *incubation period* of Carrion fever is about three weeks The onset is marked by *malaise* and *apathy* followed by a rapidly developing *anemia* and a remittent and irregular *fever* Pains in the bones and joints are common The anemia is of the *macrocytic hyperchromic type* (p 1077) and blood smears show marked anisocytosis poikilocytosis and nucleated red cells The hemoglobin may fall to 20 or 30 per cent of normal within two weeks and the red count to 1 or 2 million per cu mm or less In severe infections over 90 per cent of the red blood corpuscles may be parasitized by *Bartonella bacilliformis* and the anemia is presumably hemolytic in nature Leukocytosis is common There is no skin eruption in this stage Death results in two or three weeks in 20 to 40 per cent of cases If re

Laboratory Data

While it is generally stated that influenza is accompanied by a leukopenia a normal leukocyte count is characteristic of the uncomplicated disease The average white blood cell count at the onset and during the course of influenza is 7000 per cu mm with a range between 4000 and 12 000 Counts higher than 12 000 are generally found in patients with a complicating bacterial infection

Treatment

The availability of a concentrated vaccine prepared from Types A and B influenza grown on allantoic fluid affords opportunity for protective immunization against these type-specific organisms An initial intracutaneous test with 0 1 cc of vaccine is suggested for the detection of sensitivity If the test is negative it is our practice to inject 0 4 cc subcutaneously within twenty minutes and complete the immunization with 0.5 cc within twenty four to forty eight hours Protection lasts only for six to twelve months

Those practitioners who remember the horrors of the 1918 epidemic of influenza will probably agree with the senior author that sulfonamides (p 88) and penicillin (p 106) should be given thorough clinical trial as measures of desperation chemotherapy (p 115) in the event of a future holocaust If nothing else is accomplished antibiotics should diminish the incidence and severity of complications due to sensitive secondary invaders The efficacy of streptomycin (p 104) against gram negative organisms adds zest to the search for a successful and specific therapeutic attack

PRIMARY ATYPICAL PNEUMONIA

Primary atypical pneumonia appears to be a specific disease that is encountered much more frequently than lobar pneumonia both in civilian and in military practice In all likelihood it is the commonest type of lower respiratory infection It is usually regarded as bronchitis broncho pneumonia pneumonitis or even as an atypical lobar pneumonia

Etiology—Primary atypical pneumonia may be caused by bacteria rickettsia fungi and viruses particularly of the psittacosis group However in the largest majority of cases none of these organisms is demonstrable and it has been assumed that the causative factor is an unknown virus Proof of the hypothesis has recently been afforded by the transmission of the disease to human volunteers inoculated intranasally with pooled sputum nasal washings and bacteria free filtrates

Clinical Manifestations—The typical course of experimentally produced primary atypical pneumonia and of the spontaneous disease do not greatly differ After an incubation period of approximately twelve to fourteen days the majority of the patients complain of what appear to be the ordinary manifestations of the upper respiratory infection They note fever malaise headache anorexia stuffiness of the nose with discharge and evidences of obstructive sneezing and later cough

The physical examination is misleading in that it is unusual to find physical signs in the chest though x rays may show mild moderate or marked scattered infiltrations involving one or several lobes (Figs 62 63) At most there may be transitory and evanescent rales The chest signs

CHAPTER 18

VIRUS INFECTION GENERAL CONSIDERATIONS

VIRUSES

A LARGE number of diseases are produced by infectious agents which in general are invisible with the magnification of the ordinary microscope and which have been called filtrable since they are capable of passage through the pores of earthen filters The early concepts of virus activity which resulted in the production of an aura of mystery regarding their proclivities begin to yield to more intensive investigations referable to their size visibility and biological properties

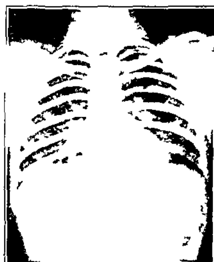
The introduction of the electron microscope capable of magnification up to 42 000 diameters has made it possible to see and to photograph viruses (Fig 61) Some such as the virus of tobacco mosaic a disease of plants have been obtained in crystalline form It has been possible also to make measurements of the size of viruses Determinations of considerable accuracy are offered by passing the organisms through graded collodion membranes whose pore size is accurately known and by the method of *ultracentrifugalization* in which the bulk is calculated from the speed of sedimentation of the particles These methods have shown that there is tremendous variation in the size of the different viruses Among the largest is the psittacosis virus which is visible with the ordinary microscope and is nearly one third the size of the staphylococcus Vaccinia virus is about one tenth the size of staphylococcus and other viruses are progressively smaller Some such as the viruses of poliomyelitis and foot and mouth disease are only twice as large as the hemoglobin molecule

The Nature of Viruses —The observations on the size and crystallization of viruses raise the fascinating problem of the nature of the substances Are they animate? Are they enzymes? Have they the properties of life ?

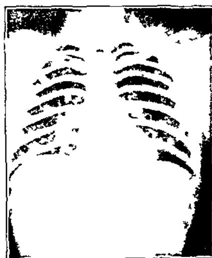
The consensus of present opinion appears to be that viruses are to be regarded as living material since they assimilate and reproduce Yet it is difficult to see how they can approach the size of protein molecules and be endowed with the properties of differentiation and specialization which would seem necessary to carry on vital functions One attempted explanation emphasizes the extreme parasitism characteristic of viruses and other pathogenic bacteria Whereas many saprophytic bacteria are capable of building protoplasm from the simplest inorganic materials in their environment the parasitic bacteria require their food already prepared for them since they have lost the enzymic mechanisms necessary for the synthesis of complex material from simple compounds The more parasitic an organism the less synthetic ability it retains within itself An extreme example of this is the influenza bacillus which requires elaborate growth factors in artificial culture since it does not have within itself the enzymes necessary to synthesize protoplasm from simple environmental food sub

purpose of therapeutic test and prevention of secondary bacterial infection with its sequels (p 2197)

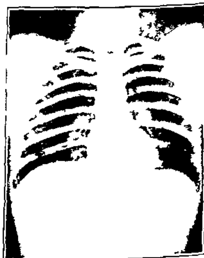
Patients with severe and intractable cough or cyanosis may be greatly relieved by *oxygen therapy* Expectorants in our experience are of no value and only *Liquor Ammonii Anisatus* is innocuous and hence worthy



September 14



September 16



September 30

Fig 62—X rays of atypical pneumonia *

of prescription In order to obtain sleep it may be necessary to give an opiate at bed time under which circumstance the hypodermic injection of codeine phosphate 15 to 30 mg (¼ to ½ grain) Dilaudid 2 mg (1/30 grain) or morphine sulfate 15 mg (¼ grain) appears justified

Convalescence is apt to be prolonged and there may be considerable post illness asthenia The latter may be lessened if the patient can be per

* Commission on Acute Respiratory Diseases J.A.M.A 1945 *127* 146

is then sealed and the egg returned to the incubator As the virus develops it produces visible lesions and may eventually kill the embryo In this way concentrated suspensions of virus are obtained They can be freed of foreign material in large part by filtration and differential centrifugalization

Immunity Reactions.—Viruses are antigenic and stimulate the production by the host of agglutinins precipitins complement fixing and virus neutralizing antibodies There is evidence that some viruses are as antigenically complex as bacteria In *vaccinia* for example agglutinogens L and S are present one heat labile and the other heat stable Both give rise to the formation of specific and separate agglutinins

The immunity resulting from virus infections is as variable as that which results from bacterial infections While it is commonly stated that virus disease results in life long immunity this is by no means invariably true The *common cold* and *influenza viruses* for example leave little or no durable immunity neither does *trachoma* or *herpes Smallpox poliomyelitis* and *measles* result in durable and relatively permanent immunity There is some evidence that in those virus diseases characterized by long lasting immunity the virus may persist in latent form in the tissues and by its continued presence stimulate and maintain tissue immunity

Diagnosis—At the present time the diagnosis of virus disease is made essentially on clinical grounds An immunologic test available to the practitioner is the *Frei reaction* for the diagnosis of lymphopathia venereum Virus can be recovered from tissues nasopharyngeal washings blood and spinal fluid but the necessary procedures are beyond the capacity of routine diagnostic laboratories *Complement fixation tests* can be done for influenza psittacosis lymphocytic choriomeningitis and the several varieties of virus encephalitis *Neutralization tests* which require laboratory animals are less easily carried out and can only be done in research laboratories

Tissue Affinities—Viruses in general exhibit special affinity for certain types of tissues and this has been used as a basis for their classification Thus it is common to speak of *neurotropic viscerotropic hepatotropic* and *dermatotropic viruses* This property has probably been overemphasized since strictly speaking a neurotropic virus attacks only nerve cells and on this basis only poliomyelitis and rabies can be considered neurotropic Equine encephalitis and other virus encephalitides attack mesodermal cells as well and are therefore pantropic Even vaccinia which produces frank lesions only in the skin actually becomes disseminated throughout the body Moreover it is not difficult to convert a hepatotropic virus such as yellow fever to a neurotropic virus by passage through mouse brain

Active and Passive Immunotherapy—*Active immunization* is successful in only a few virus diseases for a number of reasons not the least of which is the difficulty of obtaining concentrated virus in relatively pure state and free from cellular debris In most cases killed virus is inert and relatively impotent as an immunizing agent The necessity for using living

DIFFERENTIAL DIAGNOSIS OF THE

Commoner Febrile Intrathoracic Disorders

The a sociation of fever and evidences of intrathoracic disease poses a formidable diagnostic problem for the practitioner In the acute disturbances which may be aseptic he is remiss if he does not obtain sputum for bacteriologic examination by smear and culture In a certain number of instances organisms such as the coccal forms are readily demonstrated. In a larger group particularly in atypical virus infections the laboratory reports are negative Less frequently the pathologist identifies a chronic invader most notably the tubercle bacillus Hyperacute infections require the additional information that can be obtained from blood cultures If specimens are not obtained before antibiotic therapy is instituted, the bacteriologic indications may never be elucidated

In chronic intrathoracic disease even more extensive surveys are required Additionally the endoscopist may be summoned to perform bronchoscopy and pleural fluid is aspirated for bacteriologic studies and injection into guinea pigs Single and preferably serial, x rays are es ential both for diagnosis prognosis and evaluation of therapeutic procedures More elaborate examinations of sputum are required. These involve a search for fungi helminths or amebas When sputum specimens are unsatisfactory material may be obtained by bronchoscopy or the examination for tubercle bacilli is conducted on concentrated gastric contents or stool Occasionally all efforts at the identification of the etiologic factor are unrewarding and the therapeutist must proceed without knowledge of the pathogen.

	DIAGNOSTIC FEATURES
Acute Pneumonitis	May be caused by organisms other than pneumococcus and the virus of atypical pneumonia Observed with cocci (pneumococcus streptococcus staphylococcus) bacilli (pertussis typhoid tularense mucosus capsulatus glanders plague diphtheria and brucella) rickettsia (epidemic and scrub typhus and Rocky Mountain potted fever) and viruses (measles infectious mononucleosis psittacosis ornithosis choriomeningitis and influenza)
Atypical Pneumonia	Most frequent type of pneumonitis Irregular course Laboratory tests negative Resistant to therapy but low mortality X ray (p 400)
Bronchial Asthma	Bronchospasm in acute and recurrent attacks Low pyrexia Eosinophils in sputum Relief from epinephrine (p 2101)
Bronchiectasis	Chronic disturbances with acute episodes May follow acute or chronic pneumonias or persistent sinusitis May require contrast films for demonstration (p 2159)
Bronchitis	May be acute or chronic Diffuse signs but negative sputum and x rays (p 2168)
Circulatory Disturbances	With pulmonary hypostasis and edema (p 2086) With pulmonary embolization and infarction (p 2087) Take x rays Look for evidences of backward failure and thrombophlebitis of peripheral veins
Empyema Thoracis	Usually postpneumonic or with bacteremia Get x ray and cultures of blood and pus (p 2222) Consult surgeon
Eosinophilic Pneumonitis	Persistent migrating inflammation in allergic Eosinophils in sputum (p 2104)
Epidemic Pleurodynia	Acute virus disease with severe pain but no physical signs (p 403)

CHAPTER 19

VIRUS INFECTIONS RESPIRATORY

The Common Cold
Influenza
Primary Atypical Pneumonia
Epidemic Pleurodynia
Dengue Fever
Dengue like Fevers

THE COMMON COLD

THE common cold is not a single disease but is undoubtedly of multiple etiology The vast majority of colds are initiated by a virus infection Others are essentially acute bacterial infections of the nasopharynx and often represent exacerbations of chronic sinusitis and other nasopharyn geal conditions Finally the remaining colds are not infectious at all but are allergic and vasomotor reactions of the mucous membrane (p 2098)

Etiology—The upper respiratory passages teem with bacterial life and normal individuals may harbor the various varieties of the *pneumococcus* the *streptococcus* the *staphylococcus* the *Friedlander bacillus* the bacillus of *influenza* *micrococcus catarrhalis* *diphtheroids* *meningococci* the *fusiform bacillus* the *Vincent spirochete* and other bacteria which are unidentified Extensive and meticulous investigations seem to indicate that no one of these organisms is the cause of the common cold though any one may become invasive after the onset of the inflammatory process In these instances the identified bacterium is a definite secondary invader If these researches fulfill no other purpose they explain the uselessness of commercial or autogenous cold vaccines in the prophylaxis and treatment of that affliction

Immunity—The common cold does not result in any active immunity except of a transitory character Attempts to produce an artificial active immunity by the subcutaneous injection of living tissue culture virus have thus far been unsuccessful

Epidemiology—The prevalence of the common cold cannot be exaggerated The average American citizen probably averages two or three colds each year According to the records of the United States Public Health Service college students have three colds a year and government employees have two The common cold accounts for 47 per cent of all illness and 71 per cent of the respiratory diseases the average American worker loses almost three days each year because of it

Colds do not differ throughout the world There is a close parallelism between nasopharyngeal flora in isolated semitropical farming communities in Alabama in remote semiarctic trading posts in Labrador and in New York City

The incidence of colds is greatest in the fall and winter and least in the summer Age appears to play an important role in susceptibility since children under the age of 5 are most often affected From 5 to 20 years of age the incidence curve falls only to rise again to a peak at 35 after which it falls again in the older age groups The two sexes are equally affected

The common cold is transmitted by *droplet infection* from secretions of the mucous membranes of the nose and throat Infection is also transmitted indirectly by contamination of towels handkerchiefs drinking cups toys and other inanimate objects The cold is probably most infectious during the first three days of the acute illness

Neither geography nor climate appears to affect the incidence of the cold Contrary to the general impression cold weather in and of itself does not produce the cold In isolated and icebound islands such as Spitzenberg the inhabitants do not suffer from colds during the winter when the weather is most severe However in the spring when the men are brought from the mainland an epidemic of colds rapidly develops Of the climatic conditions a *sud-*

Tuberculosis	May cause acute miliary pneumonic, sub acute or chronic disturbances Check with x ray Try to identify acid fast bacillus in sputum, gastric content or stool Skin test (p 60)
Woolsorters Disease	Pulmonary anthrax. Identify organisms in sputum (p 50)

number of cases were reported in Illinois and Indiana Since the disease *occurs in the summertime it has been suspected that there is a possible vector* probably the *mosquito* but there is no definitive knowledge at the present time

Clinical Manifestations —The attack is usually initiated by a sudden onset of excruciating *muscular pain* at the site of the attachment of the diaphragm to the anterior thoracic wall The pain may be on either or both sides or in the epigastrium The patient experiences an elevation of *temperature* and a marked increase in the *rate of respiration* with a decrease in amplitude There is constant *headache* but rarely any pain in any other region

At the end of twenty four hours the pain suddenly disappears the temperature falls the patient has a profuse diaphoresis and falls into a refreshing sleep The initial attack may be followed by a recurrence of lesser severity within one to seven days

Fibrinous pleuritis is apparently a common complication Less often patients have been reported to develop *fibrinous pericarditis orchitis* and *bronchopneumonia*

See *Differential Diagnosis of Commoner Febrile Intrathoracic Disorders* (p 404)

Treatment —The treatment of Devil's Grip is purely *symptomatic* The *analgesic* drugs are administered If these fail to give adequate relief an *opiate* should be injected Some of those who have seen the disease most frequently prefer the use of *quinine sulfate* in doses of 0 2 to 0 3 gm (3 to 5 grains) every two hours

DENGUE FEVER ('BREAK-BONE FEVER')

Dengue fever is an acute infectious disease due to a filtrable virus and transmitted by the bite of infected *Aedes aegypti mosquitoes* The disease *is worldwide in distribution wherever Aedes aegypti are found* It is common in the tropics and subtropics and in the United States epidemics have occurred in the Gulf States Epidemics of dengue like influenza are remarkable for their very high attack rates and for the extraordinary rapidity with which the disease can spread Half of the population of a city may be stricken with dengue in a very short time

Etiology —The *virus* is present in the blood of patients from the day before clinical onset until the third or fourth day of the disease and the mosquito becomes infected by sucking blood during that time The mosquito then remains infective for the duration of its life

CLINICAL MANIFESTATIONS

The *incubation period* of the disease is from three to nine days The symptoms of dengue set in more rapidly than in any other infectious disease with the possible exception of influenza Patients can often recall

severity or complications of the common cold among the vaccinated and unvaccinated

Individual patients often claim to obtain a gratifying result from vaccine This is more likely the effects of chance or the greater hygienic precautions exercised by the person who is willing to go to the trouble and expense of *prophylactic inoculations* Confirmation of this viewpoint was recently obtained in a controlled series where the best results seemed to be experienced in a group whose injections consisted of sterile saline solution[1]

As a point of practical management it is our custom to employ cold vaccine only upon the insistence of the patient who is frankly told the facts as well as the additional information that we ourselves do not use these preparations in our own household

VITAMIN THERAPY

It was inevitable that the copywriters for the commercial institutions that have profited by the introduction of vitamins should stress the importance of these preparations in relation to the common cold Indeed *one bright light of the advertising world labeled* Vitamin A as the cold preventative There is now sufficient experience so that it may be stated that there is evidence to show that neither Vitamin A nor any *other* similar preparation has any influence on the incidence of colds except perhaps in those who suffer from severe clinical avitaminosis (p 616) Those who do not evidence any manifestations of vitamin deficiency might better spend their money on the purchase of food and transfer their efforts at prevention to avoidance of fellow citizens harboring the cold virus

DIET

Dietotherapy has no effect on the treatment or prevention of colds Forcing fluids drinking fruit juices emphasis on high calcium preparations and alkalinization despite the enthusiasts for each of these measures accomplish nothing in controlled observations

ULTRAVIOLET RAY

The cold virus is resistant to direct exposure to ultraviolet ray Despite this observation many patients are told that the achievement of a sun burn by artificial ultraviolet radiation will protect them from infection We are in accord with the conclusion that no reliance can be placed upon this method of therapy (ultraviolet ray) to bring about immunity from colds

DRUGS FOR PROPHYLAXIS

Many *cold specifics* are marketed *for preventive use* The most popular today is a preparation containing codeine sulfate papaverine and an antipyretic in the proportions undernoted

℞

Codeine Phosphate	0.25
Papaverine	0.5
Acetylsalicylic acid	4.25

Divide and mak 15 capsules
Sig 1 capsule every four hours as directed

DENGUE-LIKE FEVERS (PANAMA SIX DAY FEVER, BWAMBA FEVER)

There are several dengue like fevers that are observed in various parts of the World They resemble dengue in that they are of viral origin are probably transmitted by *sandflies* but may differ in their duration and in the absence of a recurring phase and the rash These include *Panama Six Day Fever* as seen in the Canal Zone *Van der Scheer Five Day Fever* of the Dutch East Indies the *Seven Day Fever* of India which differs from the leptospiral infection elsewhere described (p 360) and *Bwamba Fever* of Uganda in Africa

the community Indeed students of the public health aspects of the common cold believe that the man days lost in a given industry due to respiratory infection could be appreciably decreased if companies maintained a rule that forbade those suffering from an upper respiratory infection to continue at their work

DIET FLUIDS AND PURGES

The patient with a cold may take a normal diet and a normal amount of fluid Nothing is to be gained by purging except an increase in discomfort Forcing fluids particularly fruit juices is also of no benefit Starving a cold is a principle that has fortunately been abandoned

SWEAT BATH

The only active therapeutic measure which we advocate with any degree of enthusiasm is the *sweat bath* in the early stages of the disease If the patient can have some member of the household in attendance he should immerse himself in a tub containing water that is as hot as the skin can bear While in this tub *diaphoresis* is encouraged by sipping a warm drink such as tea or lemonade with or without added sugar and alcohol If it is possible for the afflicted to endure this heroic treatment for ten or fifteen minutes an artificial hyperpyrexia approaching 103° F may be produced When the patient has reached the limit of his endurance the water is drained out of the tub and warm towels are used for a thorough drying The body is then sponged with alcohol and the return trip to bed is accomplished

Those who do not have bathtub facilities may substitute the old fashioned *mustard foot bath* (p 3133) using the largest available pail and remembering that the active ingredient is an enzyme destroyed by temperatures higher than tepid

DRUGS

The drug treatment of the common cold depends upon the stage of the disease In the period of incubation while the discomfort is generalized the *coal tars* relieve the generalized aches and pains Locally in the nose a *vasoconstrictor* (p 2027) temporarily clears the airway by shrinking the mucous membrane and the *instillation* of oils soothes the inflamed surface

When the catarrhal phase has begun with the discharge of watery secretion one or two doses of *atropine sulfate* or *tincture of belladonna* tend to decrease the annoyance of the secretion but accomplish nothing more and may add to the discomfort by drying the throat and mouth In the purulent stage *inhalations of steam* are most grateful The addition of medication adds nothing but the odor To be effectual the steaming is done under a hood It is followed by the instillation of oil There is nothing to be gained from *external applications* to the throat or chest though some patients are more comfortable if they are provided with a light fitting jacket or sweater

Our patients are given their favorite analgesic antipyretic which they take as frequently as the need arises and discontinue when they develop unpleasant or untoward manifestations Other than the Liquor Ammoniae *Anisatus* in 30 drop doses we attempt to avoid the use of cough medi

Pathology—The lesions of measles are limited to the skin and mucous surfaces of the eyes and the respiratory tract There are edema and hyperemia of the skin with a lymphocytic accumulation about the blood vessels The inflammatory edema accounts for the characteristic swelling of the soft tissues of the face As the hyperemia and edema disappear the superficial layers of the epidermis desquamate

The conjunctivae and the mucous membranes of the nose pharynx larynx, trachea and bronchi show a catarrhal inflammation Additionally an appreciable number of patients suffer involvement of the lungs with a resultant *interstitial bronchopneumonia* In almost all fatal cases there is a secondary *bacterial pneumonitis* (p 2185)

Clinical Manifestations

Measles has an asymptomatic incubation period and a catarrhal pre-eruptive phase of invasion These are followed by the eruption with its desquamation and usually one of several complications

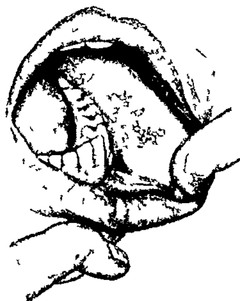


Fig 64—Koplik s spots in measles

Incubation—*In the great majority of patients the incubation period* averages ten days It may vary between eight and fourteen days but it is never less than a week and rarely as long as three weeks Since the patient becomes infective only in the last two days of the incubation period it is permissible to allow the child to continue in school and at play during the first seven days if the date of exposure is definitely known

Period of Invasion—The onset of symptoms is usually gradual with manifestations of a severe *rhinitis lacrimation* and *photophobia* The *temperature* rises gradually reaching its maximum at the time of the full eruption on the face The constitutional symptoms are not characteristic and include headache drowsiness anorexia and muscle pains A hard dry *cough* indicates the presence of catarrhal inflammation in the larynx and trachea The child frequently complains of a *sore throat* and on inspection there can be noted congestion and hyperemia of the fauces tonsils and posterior

Hecker Trumpp and Abt

t on and their blood contained *virus-neutralizing antibodies* Later it was noted that infected ferret lung tissue could produce pneumonia in mice after intranasal instillation The influenza virus can now be propagated in tissue culture and on the chorio-allantoic membranes of developing chick embryos

There are at least several and possibly *more strains* of influenza virus which are antigenically distinct The virus originally isolated is known as *influenza A* Influenza B and possible C strains have also been found The presence of these antigenic varieties complicates the problem of developing methods of active *immunization* There is at present no recognizable clinical difference in the disease produced by the various strains

Epidemiology—The pandemic of 1918–20 was studied extensively and a good deal of our knowledge of the epidemiology of influenza was acquired at that time It is by no means certain however that the characteristics of the disease as manifested then are also constant for epidemic or interepidemic influenza at present During the great pandemic which was world wide in distribution it is *estimated* that 20 000 000 people died directly or indirectly as a result of influenza or its *complications* In the United States alone 500 000 deaths resulted from the effects of the disease The attack rate was highest in children and young adults and greater in males than in females Despite the great number of deaths the case fatality rate was low Almost all the deaths were the result of pneumonia due to the virus itself or to secondary bacterial infection There were three waves in the spread of the pandemic each succeeding wave being of less magnitude

There is *no reason* to think that these epidemiological features are always true of influenza In 1928 and again in 1936–37 and 1940–41 during fairly extensive epidemics in the United States the mortality from secondary pneumonia was decidedly lower than in 1918 and 1919

Transmission—Influenza is an extraordinarily contagious disease due to universal susceptibility and the failure of one attack to produce any more than transient immunity Like the common cold it is transmitted by *droplet infection* possibly also by direct contact and contamination of food clothing and other inanimate objects handled successively by the patient and his associates Experimentally infection may be produced by spraying suspensions of virus into the air If the air at the same time is irradiated with ultraviolet light or sprayed with an *effective* concentration of an *aerosol* such as propylene glycol the virus is killed and infection prevented Such control measures are only beginning to be applied in clinical investigations but they offer bright promise for the future control of air borne infectious agents

Immunity—The duration of *immunity* following influenza is comparatively short and second attacks may occur within a few months The presence of several antigenically distinct strains of influenza virus suggests that a second attack may be the result of infection with a different variety of the virus

Pathology—Little is known of the tissue reaction in uncomplicated influenza since it is ordinarily associated with a negligible case mortality rate In experimentally infected ferret the nasal mucosa is most severely involved and there is necrosis of the surface epithelium It is probable that similar changes occur in humans and in addition there is a catarrhal inflammatory reaction throughout the whole respiratory tract producing rhinitis pharyngitis laryngitis tracheitis and bronchitis The lesions of influenza pneumonia are described elsewhere (p 2183)

Clinical Manifestations

The *incubation period* of influenza is short and probably averages two days Although *prodromal symptoms* are occasionally noted and some patients have a history of a preceding upper respiratory infection the *onset is acute* in the majority of patients *Headache* develops and is soon accompanied by *chilliness aching* and *heaviness in the back arms and legs lassitude depression* and *weakness* Within twelve to twenty four hours the *temperature rises* to 102 to 103° F., the symptoms increase and a short dry *cough* develops On the second day in an uncomplicated case the distress is at its height and the physician is summoned

Physical examination at this time reveals a patient who is acutely ill and uncomfortable He is drowsy and somewhat mentally dull The skin is hot and dry The face is flushed red and slightly swollen with slight

DIFFERENTIAL DIAGNOSIS OF THE

Commoner Generalized Maculopapular Eruptions

This type of eruption may be encountered in many of the common infectious diseas s notably measles rubella meningococcemia typhus and Rocky Mountain spotted fevers infectious mononucleosis and syphilis A definite diagnosis of the nature of the invading organism becomes apparent in most instances by careful clinical ob ervation, blood cultures s ro logical reactions and the examination of the hemogram

Other examples of maculopapular eruption result from the presence of descriptive dermatoses such as the frequently encountered psoriasis pityriasis rosea lichen planus, tinea versicolor and erythema multiforme For the recognition of these the clinician is dependent upon the skill with which he makes ob ervation The less frequently encou tered causes of the generalized maculopapular eruptions are mostly infectious and they include dengue leprosy sarcoidosis and frambesia tropica

CAUSE	DIAGNOSTIC FEATURES
Dengue	Macular eruption first seen on dorsum of hands and feet Rapid evolution and involution History of epidemic (p 406)
Dermatitis Medicamentosa	History of u e of drugs (p 3335)
Ephelides	Freckles Afebrile
Erythema Multiforme	May present discoid red macules and papules together with nodules and vesicles (p 3374) Usually afebrile
Fifth Disease	Macular eruption of face in children (p 418) No Koplik spots Spreads to body and extremities
Frambesia Tropica	Generalized papular eruption following extra genital spirochetal implant (p 351) Refer to expert for darkfield microscopy Wassermann positive
Infectious Mononucleosis	Diffu e maculopapular eruption with positive hemogram and heterophile reaction (p 468) Generalized lymphadenopathy False positive Wassermann (p 337)
Leprosy	Anesthetic macules and nodules Thickening of ulna nerves (p 274) Usually afebrile
Lichen Planus	Multiple flat violaceous papules Intense itching On flexor surfaces (p 3389) Afebrile
Measles	Raised macular papular eruption first seen behind ears usually in children Preceded by Koplik spots of buccal mucosa (p 411) Later spreads to face neck trunk and extremities Brawny desquamation False positive Wassermann (p 337)
Meningococcemia	Acute febrile illness with diffuse maculopapular eruption later becoming purpuric or petechial Positive blood culture and spinal fluid (p 211)
Papulonecrotic Tuberculid	Crops of papules of extensor surfaces or trunk Later crusting and necrosis B opsy (p 3265)
Pityriasis Rosea	Herald patch and generalized pink scaly macules Inten e pruritus (p 3410) Afebrile
Psoriasis	Chronic recurrent dermatosis with scaling papules and intense pruritus On extensor surfaces (p 3414) Afebrile

LABORATORY DIAGNOSTIC METHODS

Laboratory technics are as yet not available to the practitioner but there is reason to hope that simplified procedures may soon be introduced so that an etiological diagnosis of influenza can be made The precise laboratory diagnosis of influenza involves the following unusual procedures (1) *Nasal washings* are obtained early in the disease and instilled intranasally into ferrets which develop a characteristic respiratory infection Upon recovery *antibodies* develop which neutralize known influenza virus (2) *Tissue cultures or eggs* are infected and propagate the virus By means of *mouse protection tests* the strain of influenza virus can then be identified (3) *Convalescent serum* from patients recently recovered from influenza inhibits the agglutination of chicken red cells by virus infected amniotic chick egg fluid (4) Patients who recover from influenza develop *virus neutralizing and complement fixing antibodies* By comparing the titer of blood serum obtained during the acute illness with the titer obtained during convalescence it can be demonstrated that antibodies develop as a result of the specific infection Thus a diagnosis can be made in retrospect

COURSE

Patients with uncomplicated influenza have fever and symptoms for two to six days or an average of 5 days The temperature may show all manner of variations but is commonly highest twenty four to thirty six hours after onset In a considerable number of patients the temperature exhibits two cycles It falls to normal on the third day rises again and finally returns to normal on the fifth or sixth day An irregular fever with daily spiking is also seen A number of patients never have fever above 101° and in every epidemic some are seen who remain entirely afebrile yet complain of headache dry cough nasal obstruction and muscular pain Presumably these are atypical mild manifestations of the disease yet clinically they are indistinguishable from infection with the common cold Patients with bronchiolitis have a more prolonged course with fever for a week or more and on the whole their symptoms are more pronounced than those of patients with normal chest findings or with signs of tracheobronchitis

COMPLICATIONS

In a small number of patients secondary bacterial infection develops leading to *purulent bronchitis* The common nasopharyngeal organisms such as *H influenzae* pneumococci staphylococci and streptococci may be cultured from the sputum Other purulent complications such as sinusitis and otitis media are common in children

The severest type of influenza is complicated by *pneumonia* In the 1918–1920 pandemic about 15 per cent of the patients suffered from this type of disease but in recent epidemics only 5 per cent have been of this nature Pneumonia occurring in the course of influenza may be primarily due to the influenza virus itself or may be due to secondary bacterial infection with staphylococci pneumococci *H influenzae* or hemolytic streptococci Influenzal pneumonia is discussed more fully in another section (p 2189)

DIFFERENTIAL DIAGNOSIS OF THE

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may be completely missed or they may persist The temperature may never be significantly elevated or it may rise to as high as 105° The fever may be transitory or it may persist for several weeks

The laboratory data are completely misleading The blood counts are normal Blood cultures reveal no growth Sputum examinations disclose only the ordinary flora Curious laboratory phenomena that are not of significant diagnostic value are the development of cold agglutinins to group O human red cells and of a false positive Wassermann reaction

Differential Diagnosis—The diagnosis of primary atypical pneumonia is completely a clinical discipline There seems very little doubt that the majority of the milder examples and even those of moderate severity are completely missed Oftentimes the patient does not even consult the doctor believing he has a heavy or persistent cold In instances where the physician is summoned it is unlikely that the condition can be recognized unless x rays are taken at the time of the visit when the patient is at home or after convalescence when the patient visits the office Since there are rarely facilities for roentgenography in the home and patients do not customarily come to the office for an x ray examination after recovery from a respiratory infection the disease passes without recognition

In the severe or moderately prolonged instances of the disease which are perhaps unusual rather than common the physician may consider particularly the diagnoses of lobar pneumonia typhoid fever and tuberculosis Lobar pneumonia is characterized by the much more abrupt onset more frequent herpes the presence of leukocytosis and by the growth of pathogenic pneumococci from sputum or blood The diagnostic dilemma is most satisfactorily resolved by the therapeutic test since pneumococcus infections respond specifically to sulfonamides or penicillin whereas atypical pneumonia is uninfluenced

Differentiation from typhoid fever and tuberculosis is established wholly on laboratory grounds Absence of typhoid bacteremia or agglutinins and failure to find the tubercle bacilli in sputum stomach washings or stools suggest that prolonged fever with persistent lung signs is most likely a primary atypical pneumonia

Complications and Prognosis—Primary atypical pneumonia rarely has complications and very rarely terminates fatally It is impossible to give statistics for the incidence of untoward sequels since the vast majority of the infections are unrecognized and any figures would be weighted on the side of being far too gloomy

The most treacherous of the sequels are progression toward bronchiectasis necrotizing pneumonitis (p 2195) pulmonary abscess pleural effusion pneumothorax or empyema (p 2222) In the majority if not all instances the sequels are probably due to complicating secondary infection which would have been preventable by nursing care and antibiotic therapy

Treatment—The treatment of primary atypical pneumonia resolves itself into nursing care alone in all but the most protracted and severe examples Neither *sulfonamides* nor *penicillin* has any prophylactic or curative value so far as the infection itself is concerned Nevertheless either or both drugs should be given those patients who are severely ill or whose temperatures last beyond a week This practice serves the dual

and constitutional symptoms increase They reach their maximal development at about the time that the rash approaches 'full bloom' on the face at which time the patient presents a characteristic appearance He is fretful and 'measly' The face is swollen and distorted the conjunctivae are irritated and there is annoying photophobia The skin itches and a hacking cough soreness on swallowing and pain in the cervical lymph nodes add to the general discomfort The patient has no desire to eat or drink Attempts to force nutrition are met with irritability and annoyance

As the rash begins to fade, the temperature falls and reaches normal in two or three days The catarrhal symptoms subside with the fall in temperature and in the absence of complications the patient is convalescent within a few days

Desquamation —Desquamation begins almost as soon as the rash fades It appears first on the face and neck later over the rest of the body The flakes are fine and branlike in contrast to the larger sheets that are seen in scarlet fever (p 178) Desquamation is usually complete in five to ten days The amount of scaling is proportional to the intensity of the rash

Variants —The average and usual course of measles as previously described is most often seen in children over the age of three who have not received any form of specific therapy The younger children are more apt to have severe manifestations Older persons may follow milder or severer courses

The severe cases of measles are those which are complicated by *bronchopneumonia otitis media* or some other of the communicable diseases In these patients the temperature remains elevated after the rash has begun to fade or the fever recurs after the normal level has been established Examination reveals the presence of some complicating process in the throat ears eyes or head

Modified Measles —In the milder manifestations the temperature may never rise above 102° F and may remain elevated for no more than three or four days The catarrhal symptoms are mild and the rash is faint This mild course is not unusual in patients who have received specific serum therapy and corresponds to 'modified measles' Complications are rarely observed

COMPLICATIONS

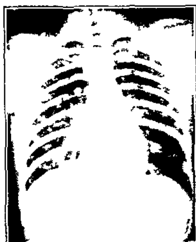
Considering the incidence of measles serious complications are relatively uncommon Those that are most usually encountered *include otitis* media cervical adenitis and bronchopneumonia

Cervical adenitis frequently accompanies measles but rarely proceeds to suppuration *Otitis media* is commonly encountered but is neither as frequent nor as severe as the type which complicates scarlet fever

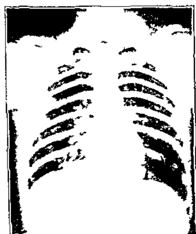
The most serious sequel of measles is a *bronchopneumonia* due to a superimposed hemolytic streptococcal or pneumococcal invasion These invasions account for 90 per cent of deaths that are ascribed to measles They are to be suspected whenever fever persists for more than a day or two after the rash has begun to fade The management of measles pneumonia is elsewhere considered (p 2188) See *Differential Diagnosis of Commoner Febrile Intrathoracic Disorders* (p 404)

Meningitis and *encephalitis* with characteristic symptoms may follow measles These complications are more apt to be seen in institutional

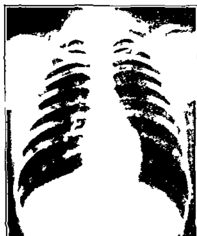
suaded to eat liberally throughout the illness The use of alcohol in the form of sherry or a cocktail before luncheon and dinner provides the best appetite stimulus The patient and the family may be assured that neither the beverage nor the high calory feedings including meat have any tendency to elevate or perpetuate fever



September 2



September 25



October 4

Fig 63 —X rays of atypical pneumonia

EPIDEMIC PLEURODYNIA (DEVIL S GRIP EPIDEMIC MYALGIA BORNHOLM DISEASE)

Epidemic pleurodynia is an acute infectious disease of unknown origin There is some evidence that the disturbance is of *virus origin* It occurs more often in the Nordic States than in America although in 1934 a

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ACTIVE IMMUNIZATION

The cultivation of measles virus on the membranes of the developing chick embryo raises the possibility that the future will soon disclose an antigen with which to attempt artificial active immunization

PASSIVE IMMUNIZATION

Human Measles Immune Serum (U S P) is obtained from convalescents It is of definite value in the prevention of measles If given intramuscularly before the 7th day after exposure 49 per cent of the children will escape the disease and only 0 7 per cent will develop the illness in its usual form The rest succumb to a modified measles which is so mild that it is often difficult to recognize The recommended dose of human serum is 5 cc for children up to the age of one year 10 cc for those up to the age of 10 years and 15 to 20 cc thereafter In a small number of instances the injection of serum is followed by chill and fever

Inasmuch as there is often some difficulty in obtaining the human convalescent measles serum *Human Immune Globulin (U S P)* has been made commercially available and is also obtainable from many local health agencies In this product antibodies protective against measles have been extracted from normal human placenta or from whole blood after the removal of plasma for injection purposes The final product is standardized according to the requirements of the National Institute of Health and can be injected intramuscularly in doses of 2 to 4 cc The modification of measles by immune globulin is as described for the convalescent serum Reactions may occur both systemically and locally

The passive immunity that is acquired from these substances persists for only a few weeks The degree to which the disease is prevented or modified depends primarily on the time at which the immune substance is injected If given in adequate dosage during the first four days after exposure measles will almost surely be prevented If given between the fifth and ninth days a mild modified measles results In modified measles the incubation period is prolonged the attack is mild but typical complications are rare and a firm and permanent immunity is accomplished

Human gamma globulin prepared from plasma promises to replace all other remedies Intramuscular injections of 0 1 to 0 75 cc per lb are best made on the fifth day after exposure Children less than 5 years of age require 2 5 cc and double this amount is needed for older patients Reactions are negligible and a recent experience revealed complete protection in 79 per cent of the exposed modified measles in 21 per cent and regular measles in none! Meanwhile 83 per cent of a control group developed regular measles many with complications

ANTI INFECTIVE AGENTS

Sulfonamides and penicillin have no effect on measles When complications threaten they should be administered as a form of *prophylactic chemotherapy* This procedure is especially advisable in young infants and debilitated children who are the most prone to develop *pneumonitis*

Furunculosis of Lungs	With or following staphylococcemia Get blood culture and x ray (p 2212)
Hodgkin s Disease	Granulomas often of mediastinal lymph nodes with fever eosinophilia and lymphadenopathy Get biopsy (p 1138) Note response to x ray
Lobar Pneumonia	Signs of consolidation in acute illne s Get smears and cultures of sputum and blood culture Usually pneumococcal Specific re sponse to antibiotics (p 2171)
Lung Abscess	May be putrid or aputrid Former usually bronchogenic after tonsillectomy or tooth extraction Latter often postpneumonic Note odor to sputum Get x rays and sputum smears and cultures (p 2214) Consult surgeon.
Mechanical Lesions	With atelectasis (p 2052) massive collapse of lung (p 2053) hemothorax (p 2032) and spontaneous or therapeutic pneumothorax (p 2035) Check signs with x ray
Mediastinal Lymphadenopathy	Usually tuberculous but may be due to brucellosis pulmonary mycosis Hodgkin s disease or neoplasm. Get several films spu tum and skin tests (p 59)
Mediastinitis	May be acute or chronic May follow pene trating or perforating lesions of trachea or esophagus May accompany septic sore throat (p 185)
Neoplastic Disease	From secondary infection associated with benign or malignant tumors of tracheobronchial tree (p 2077) In miliary carcinomatosis (p 2081) and lymphoblastoma (p 1137) Get bronchoscopic biopsy
Pleuritis	May be acute subacute or chronic and fibrinous or effusive (p 2032) Check signs with x ray Aspirate fluid and examine cytologically bacteriologically and by guinea pig injection
Pneumoconiosis	In dust diseases as occupational hazard Look for superimposed tuberculosis Get x rays (p 2065)
Pulmonary Amebiasis	Suppuration due to E histolytica Get x rays and seek trophozoites or cysts in sputum (p 528) Specific response to emetine
Pulmonary Helminthiasis	Lung flukes and echinococcosis (hydatid disease) Get x rays and search sputum for ova and hooklets (p 1894) Skin test (p 59)
Pulmonary Mycoses	Especially actinomycosis coccidioidomycosis moniliasis torulosis and blastomycosis Check with x ray sputum smears and cultures and skin tests (p 59)
Pulmonary Spirochetosis	Chronic infection with demonstration of organisms in sputum (p 50) Note response to arsenicals and penicillin
Rheumatic Fever	With polyarthritis and carditis in young Usualy a pleural effusion subsiding after salicylate (p 186)

CONTINUED

The *temperature* rarely exceeds 101° F and usually falls to normal shortly after the appearance of the eruption The chief discomfort is moderate itching of the skin though there may be a mild conjunctivitis and some persistence of the coryza *Enlargement of the postauricular occipital and cervical lymph nodes* is a constant feature of the disease The lymphadenitis invariably subsides without suppuration

In German measles the leukocyte count is normal or somewhat low The presence of a leukocytosis suggests the possibility of a mild atypical scarlet fever Rubella in early pregnancy may be responsible for con en ital fetal defects especially cardiac anomalies and cataracts

Diagnosis

The chief difficulty in rubella is the problem of diagnosis The disease has neither mortality nor complications In an epidemic the recognition of the condition is simplified by the history of exposure the mildness of the discomfort and the prominent lymphadenopathy Sporadic cases are difficult of recognition and should be suspected of being mild atypical manifestations of scarlet fever or measles Typical *scarlet fever* has a shorter incubation period more definite inflammatory manifestations in the pharynx and tongue and a leukocytosis Mild cases of scarlet fever with low temperatures and mild local signs may be very confusing except that the rash invariably spares the face and is followed by more marked desquamation The *Schultz Charlton reaction* (p 179) definitively differentiates the two conditions

Mild measles is very likely to be confused with rubella if the Koplik spots have not been observed The longer prodromal period the more marked symptoms of coryza and cough and the slower evolution of the measles rash are helpful points in the differential diagnosis

See *Differential Diagnosis of Eruptive Fevers* (pp 172 174)

Treatment

German measles requires isolation until the disappearance of the rash Therapeutic abortion (p 2649) merits consideration in early pregnancy

FOURTH DISEASE (FILATOW DUKES DISEASE)

In England and the rest of Europe fourth disease is described as a *mild fever* of short duration with a *generalized scarlatiniform eruption* While some claim that this is a specific disease entity it is the present consensus of opinion that *fourth disease is merely a variety of German measles* in which the rash more closely resembles scarlet fever The *Schultz Charlton reaction* is of invaluable assistance in excluding the possibility of mild scarlet fever

See *Differential Diagnosis of Eruptive Fevers* (pp 172 174)

Fourth disease requires no therapy other than isolation until the eruption fades

FIFTH DISEASE (ERYTHEMA INFECTIOSUM)

Fifth disease is an eruptive condition that has been described in Europe If it exists in the United States it is largely unrecognized and we have

the onset to within an hour The disease begins with severe *headache pain in the eyeballs* and intense pain in the muscles and tendons about the joints The pain is especially severe in the back hence the old name *break bone fever* The *temperature* rises rapidly to 103° F or higher but the pulse rate is not accelerated in proportion to the fever and after three or four days a decided bradycardia may be present Glandular enlargement is common in some epidemics Epistaxis is the chief complication

In its course the disease usually exhibits two febrile peaks (*saddle back temperature curve*) with exacerbation of symptoms in each period The fever is usually at its height shortly after onset and then falls toward normal The afebrile intermission lasts from twelve hours to three days On the third or fourth day there is a second rise of temperature and the backache and other symptoms recur This attack is usually milder When the temperature returns to normal for the second time convalescence sets in and it may be prolonged

Eruption —At the onset there is often an initial rash consisting only of a transient blotchy erythema or congestion of the face During the second febrile period on the fourth to sixth day of illness the terminal rash develops This is the most characteristic feature of the disease It usually resembles the eruption of measles but is not so dusky red Occasionally it is punctate like the scarlet fever rash It begins on the dorsal surfaces of the hands and feet spreads up the forearms and legs and later involves the face and trunk The eruption may be very fleeting or persist for as long as three days It is accompanied by itching and followed by desquamation See *Differential Diagnosis of Eruptive Fevers* (pp 192 194)

Variations —Epidemics differ in the prominence of certain features of the disease In some outbreaks the eruptions have been very transitory and mild in others glandular enlargement is outstanding Bradycardia has been characteristic of most recent epidemics In some there has been only one febrile peak and the saddle back temperature curve was not seen

Pathology and Diagnosis

The pathology is unknown since the mortality is almost negligible

There are no specific diagnostic aids *Influenza malaria yellow fever* and other acute febrile diseases can be differentiated on clinical and laboratory grounds A characteristic of dengue fever which is of diagnostic help is the regular and marked *leukopenia* By the fourth or fifth day the white count is down to about 2000 with depression chiefly of the granulocytes

Immunity and Treatment

There is apparently no natural immunity to dengue but one attack of the disease usually confers a solid immunity for a long time Second attacks do occur however but are rare The prevention of dengue fever like malaria is closely related to the problem of mosquito control Vaccines have been tried and are reported to confer temporary immunity

Treatment is entirely symptomatic

The *eruption* appears two to five days after onset at the time the fever falls to normal It is first noted on the neck and trunk It may be sparse or profuse rapidly covering most of the body It lasts from a few hours to two days and then disappears completely without leaving pigmentation or producing desquamation The rash is rubelliform rather than morbilliform The lesions are pale or rose red macules without elevation They are 2 to 3 mm in size and fade on pressure The rash is indistinguishable from that of rubella but differs from the measles eruption in that it is not elevated A characteristic feature of the disease is the marked *leukopenia* The total white count may be as low as 3500 per cu mm with a depression of the granulocytes and a relative increase of the lymphocytes which may account for 70 to 80 per cent of the total white cell count The disease has neither complications nor mortality

During the pre eruptive stage the diagnosis involves differentiation from other febrile diseases which are ruled out by the completely negative physical examination Following the appearance of the rash there may be confusion with *measles* and *rubella* *Measles* is preceded by Koplik spots and a prodromal fever which is still present at the time that the eruption appears The rash is elevated and is present on the face whereas the eruption of roseola infantum spares the nose and cheeks though it may involve the forehead *German measles* affects older children or adults and the post auricular and cervical lymphadenopathy are much more prominent

See *Differential Diagnosis of Eruptive Fevers* (pp 172 174)

TREATMENT

Treatment is entirely symptomatic

CHICKENPOX (VARICELLA)

Chickenpox is characterized by a generalized vesicular eruption mild constitutional reactions and a benign course with few complications or sequels It is a common highly communicable acute infectious process

Etiology—The causative agent of varicella undoubtedly is a *filtrable virus* present in the fluid of the vesicles the lesions of the mucous membranes and possibly in the crusts It has not been possible to reproduce chickenpox in laboratory animals but the clinical disease has been caused by the inoculation of susceptible children with bacteria free vesicle fluid Thus far the infectious agent has not been grown in tissue culture

Chickenpox and Herpes Zoster—Many observations suggest that herpes zoster and chickenpox are closely related and most clinicians believe that the two *diseases are* different manifestations of a single infection The suggestive evidence includes the following data. (1) Numerous instances have occurred in which chickenpox followed exposure to herpes zoster (2) Herpes zoster may with lesser frequency follow exposure to chickenpox (3) The successive appearance of herpes zoster and chickenpox in the same patient has been described (4) A single complement fixing antibody is reported to be demonstrable in both diseases (5) *Experimental* infection with one disease results in immunity to the other

Epidemiology—Chickenpox is endemic throughout the world There is apparently *universal susceptibility* It occurs infrequently in the newborn possibly because of a passive immunity that has been transferred from the mother Although second attacks *have* been reported a single infection usually confers *lifelong immunity* and for this reason chickenpox is essentially a disease of childhood

Transmission is presumably by *droplet* or *direct contact* infection It is not known whether healthy persons or fomites can transmit the virus but the disease should be regarded as communicable from the onset of symptoms until the disapperance of the crusted lesions a period which may vary from one to three weeks

CHAPTER 20

VIRUS INFECTIONS DERMOTROPIC

MEASLES (MORBILLI ROSEOLA)

Measles is a widely prevalent acute eruptive and communicable di ease Ordinarily a benign infection with a low mortality it may be fol lowed particularly in infants by bronchopneumonia and other bacterial complications producing a high case fatality rate

Et ology—M asles is almost certainly du to a *filtrable virus* wh h can be grown on the chorio allantoic membrane of fertile hen-eggs and it s infectious for monkeys The inocu lat on of mo keys with the blood or bacteria free nasal washings taken from pat ents with easles during the pre-erupt ve and early eruptive stages produces in these animals a macu l rash leukopenia and lesions that sugg st the appearance of the Kopl k spots

Ep d m ol gy—M asles is *endemic* in urban commun t es throughout the wo ld Its prevalence varies from year to year tending to exhibit well marked peaks of frequ ncy every two or thre years depend ng upon the immune status of the populat on Despite fluctuation n preval nce the disease is ne er e tirely ab ent f om large cities but in isolated and rural areas it may be inconspicu us for several years at a t me and then reappear n epidemic form

In cities almo t all persons contract the dise e before reaching adult l fe wh le in rural ar a it is not rare to cape nfection These differenc do ot reflect any alterat on in suscep tibil ty but ar the effect of variations in exposure During World War I the men who con tracted measles in army camps were almost all from ru al ar as

Sex and col r play no role in the susc ptit lity to measl s Tl e season of greatest prev l ce is the late winte and early spr ng particula ly the months of March and April

Tra sm s o —Measle s communic ble during the last two days of the incubation period luring th prod mal pr e uptive atarrhal stag and for about five days after the initial pp a ance of the rash Th desquamated skin is not infectious It is safe to regard th p t ent as noninfectious when the a h has definitely begun to fade The spread of measles is facil tat d by the fact that the d ase is most commun able several days before the app ar ce of the ash at a time wh n the child is frequ ntly ambulatory and at school

The spr ad of measles tak s place by d rect but brief contact and it may be d seminated by the air borne transmiss on of dried dropl ts d scharged from the throat

Immun ty—There is almost *un sal susc ptibility* to measles Attack rates as h gh as 95 per cent have o curred am o g u p otected children exposed in the course of an institutional ep d m c In general one attack of the disease confers a *lifelong immun ty* The durability of the mmunity is not related to the severity of the attack Second infections are described but must l e ext emely ra e

Infants up to the age of 6 months are well protected by pass ve transfer of immunity f om the mother but newborn infants whose mothers are not mmune may develop the disease t birth Measles has been observed in the newborn whose mother was uffering from the d s a e at the time of p rturition

DIFFERENTIAL DIAGNOSIS OF THE

Commoner Generalized Vesicular and Pustular Eruptions

Other than chickenpox and smallpox generalized vesicular and pustular eruptions are un commonly encountered in clinical medicine It is only rarely that syphilis impetigo herpes or contact dermatitis spreads to involve the entire body Except in syphilis the laboratory gives minimum assistance under these conditions and the practitioner is dependent almost wholly upon his clinical acumen

	DIAGNOSTIC FEATURES
Chickenpox	Acute infection with pleomorphic mono locular vesicles first seen on body (p 420)
Dermatitis Herpetiformis	Rare symmetrical dermatosis with grouped papules vesicles bullae and pigmentation (p 3371)
Dermatitis Medicamentosa	Pustules particularly after iodide bromid and antimony (p 3335)
Dermatitis Venenata	Vesicular eruption with intense itching from contactual substances especially poison ivy (p 3330)
Dermatitis Exfoliativa Neonatorum	Generalized form of impetigo contagiosa in newborn (p 3252)
Dermatophytids	Vesicular dermatophytids may accompany ringworm of hands and feet (p 3299)
Erythema Multiforme	Widespread skin and mucosal lesions may be vesicular as well as macular and papular (p 3375)
Foot and Mouth Disease	Vesicular eruption of virus origin Involves mouth hands and feet (p 437)
Generalized Vaccinia	Vesiculopustular eruption associated with in oculation of cowpox vaccine (p 428)
Glanders	Generalized pustular eruption containing chocolate colored pus in persons handling horses Get skin test and culture for M mallei (p 327)
Herpes	Usually localized vesicular eruption in simplex and zoster varieties Rarely generalized as in herpes gestationis in pregnancy (p 433)
Hydroa Estivale	Vesicular and bullous lesions in children sensitive to sunlight
Keratosis Blennorrhagica	Vesiculopapular eruption with gonorrheal in fection (p 3257)
Miliaria	Inflammatory vesicles and papules with itching
Molluscum Contagiosum	Umbilicated vesicles of virus origin Predilec tion for face trunk and genitals (p 3287)
Pemphigus	In early stages eruption may be vesicular be fore formation of bullae (p 3405)
Smallpox	Acute infection with monomorphic polyloc ular vesicles and pustules spreading from face to body (p 424)
Solar Dermatitis	Sunburn (p 3140)
Staphylococcemia	Generalized furunculosis with bacteremia (p 153)

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CHAPTER 20

VIRUS INFECTIONS: DERMOTROPIC

MEASLES (MORBILLI, ROSEOLA)

MEASLES is a widely prevalent acute eruptive and communicable disease. Ordinarily a benign infection with a low mortality, it may be followed, particularly in infants, by bronchopneumonia and other bacterial complications producing a high case fatality rate.

Etiology.—Measles is almost certainly due to a *filtrable virus* which can be grown on the chorio-allantoic membrane of fertile hen-eggs and it is infectious for monkeys. The inoculation of monkeys with the blood or bacteria-free nasal washings taken from patients with measles during the pre-eruptive and early eruptive stages produces in these animals a macular rash, leukopenia and lesions that suggest the appearance of the Koplik spots.

Epidemiology.—Measles is *endemic* in urban communities throughout the world. Its prevalence varies from year to year tending to exhibit well marked peaks of frequency every two or three years depending upon the immune status of the population. Despite fluctuations in prevalence the disease is never entirely absent from large cities, but in isolated and rural areas it may be inconspicuous for several years at a time and then reappear in epidemic form.

In cities almost all persons contract the disease before reaching adult life while in rural areas it is not rare to escape infection. These differences do not reflect any alteration in susceptibility but are the effect of variations in exposure. During World War I the men who contracted measles in army camps were almost all from rural areas.

Sex and color play no role in the susceptibility to measles. The season of greatest prevalence is the late winter and early spring, particularly the months of March and April.

Transmission.—Measles is communicable during the last two days of the incubation period, during the prodromal pre-eruptive catarrhal stage and for about five days after the initial appearance of the rash. The desquamated skin is not infectious. It is safe to regard the patient as noninfectious when the rash has definitely begun to fade. The spread of measles is facilitated by the fact that the disease is most communicable several days before the appearance of the rash at a time when the child is frequently ambulatory and at school.

The spread of measles takes place by direct but brief contact and it may be disseminated by the air-borne transmission of dried droplets discharged from the throat.

Immunity.—There is almost *universal susceptibility* to measles. Attack rates as high as 95 per cent have occurred among unprotected children exposed in the course of an institutional epidemic. In general one attack of the disease confers a *lifelong immunity*. The durability of the immunity is not related to the severity of the attack. Second infections are described but must be extremely rare.

Infants up to the age of 6 months are well protected by passive transfer of immunity from the mother but newborn infants whose mothers are not immune may develop the disease at birth. Measles has been observed in the newborn whose mother was suffering from the disease at the time of parturition.

DIFFERENTIAL DIAGNOSIS OF THE

Commoner Generalized Vesicular and Pustular Eruptions

Other than chickenpox and smallpox generalized vesicular and pustular eruptions are uncommonly encountered in clinical medicine It is only rarely that syphilis impetigo herpes or contact dermatitis spreads to involve the entire body Except in syphilis the laboratory gives minimum assistance under these conditions and the practitioner is dependent almost wholly upon his clinical acumen

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Solar Dermatitis	Sunburn (p 3140)
Staphylococcemia	Generalized furunculosis with bacteremia (p 153)

CONTINUED

pharyngeal wall Often at this time there is a characteristic *congestion of the conjunctival vessels* a finding which frequently arouses the suspicion of the astute practitioner

Koplik Spots —One or two days following the onset of symptoms and at least twenty four hours before the cutaneous eruption develops the Koplik spots are to be seen as tiny pinpoint bluish white lesions surrounded by a narrow red areola The earliest eruption *is seen on the buccal mucosa* opposite the molar teeth Within twenty four hours the entire buccal mucosa and the gums become peppered with these tiny spots

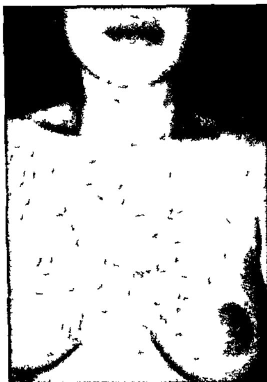


Fig 6 —The rash of measles

The Koplik spots are *pathognomonic of measles* and must be specifically sought using a good source of illumination preferably daylight They usually fade at the time that the eruption appears in contradistinction to the larger white spots of thrush or the yellow vesicular lesions of *aphthous stomatitis* (p 1695)

The Eruption —The characteristic eruption of measles appears two to four days following the beginning of the prodromal catarrhal phase The rash appears first behind the ears and on the forehead at the roots of the hair line Later it spreads to the face and neck and within the next two days spreads over the trunk the extremities being the last portion of the body to be involved The full development of the measles rash which

Prognosis

Chickenpox is ordinarily a *benign* disease The mortality rate in 2,00 cases was 0 4 per cent The rare deaths have most often resulted from secondary bacterial infection with the development of pneumonia or septicemia or from encephalitis

Prevention

Active immunization has not been widely adopted because chickenpox is so mild and benign that artificial immunization does not seem worth while except in unusual circumstances The procedure can be carried out by the intradermal inoculation of fluid obtained from chickenpox vesicles which may be followed by the development of an abortive mild form of the disease Vesicle fluid has also been injected intravenously with immunity apparently resulting



Fig 68 —Smallpox

Passive immunization is also possible by the intramuscular injection of convalescent serum during the incubation period

The use of *ultraviolet light sterilization* of the air of hospital wards for children is being evaluated Preliminary results indicate that the method is extremely effective in controlling the otherwise inevitable spread of chickenpox from one patient to another

Treatment

Ordinarily *symptomatic treatment* is required Care is taken to prevent bacterial infection of the skin lesions Infants and young children must be restrained from scratching If bacterial infection of the pocks does occur *penicillin* is applied in ointment form or given by intramuscular injection

SMALLPOX (VARIOLA ALASTRIM COTTONPOX PARA SMALLPOX)

Smallpox is a highly communicable disease which in the past was frequently encountered in a highly virulent form Although the affliction

Rat Bite Fever	Maculopapular eruption of chest and arms after bite Identify spirochetes by darkfield after lymph node aspiration. (p 36..)
Rocky Mountain Spotted Fever	Acute febrile illness with lesions fir t on wrists and ankles later spreading to body Weil Felix positive (p 372)
Rubella	Acute transitory maculopapular eruption usually in children (p 417) Marked posterior cervical lymphadenopathy No enanthem Spreads from face to body and extremities
Sarcoidosis	Brownish nodules or papules especially of face Biopsy (p 327)
Syphilis	Macular or papular syphiloderm May be plantar and palmar Darkfield and serology positive (p 331)
Tinea Versicolor	Tan to brown scaling macules due to fungus Afebrile
Tularemia	Acute febrile illness after handling rodents Maculopapular eruption becoming pustular History of tick bite Positive blood culture agglutinins or skin test (p 323)
Typhoid Fever	Roseola on abdomen in second week of ill ness Fade on pressure Positive blood or stool cultures and specific agglutination (p 225)
Typhus Fever	Acute febrile di ease with macules of axillae and loins later spreading to abdomen che t and back. Weil Felix test positive in serum (p 372)
Urticaria Pigmentosa	Pigmented macules which form wheal after rubbing Afebrile Biopsy (p 3158)
Xeroderma Pigmentosum	Pigmented macules with areas of atrophy telangiectases and kerato es on exposed parts after olar exposure Afebrile Precancerous Biopsy (p 3158)

covers the entire body including the palms and soles usually takes thirty six to seventy two hours though there are considerable variations By the time the eruption has completely developed the rash has begun to fade on the face See *Differential Diagnosis of Eruptive Fevers* (pp 172 174)

The individual lesions are pinhead in size scattered few in number and of pinkish color At first they are *macular* but as they develop they become raised and *maculopapular* Their numbers increase greatly as they cover the body but each is usually separated from the others by areas of normal skin though they may become confluent The rash becomes progres sively darker until by the fifth or sixth day it is brownish As it fades the skin remains discolored for five to ten days longer The eruption dis appears in the same order as it developed

Many departures from the typical appearance are manifest The rash may develop rapidly and cover the entire body in less than a day It may be confluent and somewhat hemorrhagic It may be sparse and consist only of scattered macules These variants are in contrast to the constancy of the Koplik spots whose *importance in diagnosis cannot be overestimated*

Local and Constitutional Symptoms—During the first twenty four to forty eight hours following the initial appearance of the rash the local

as small *erythematous macules* Within a matter of hours these become distinctly raised or papular The *papules* are small and firm and seem fairly deeply imbedded in the skin producing the characteristic *shotty feeling* The lesions increase in size and by about the sixth day become *vesicular* As fluid accumulates the center of the lesion remains depressed resulting in an *umbilicated vesicle* At first the fluid is clear but in another day or two it becomes distinctly *pustular* At the height of the eruption the *pustules are split pea size and of a green or grayish yellow color* The pustular character of the fluid is the result of the accumulation of cellular debris and does not represent bacterial infection although this may also occur In contrast to the vesicular lesion of chickenpox individual pustules are multilocular and pricking one corner with a needle does not ordinarily evacuate all its contents

The order of appearance of the eruption and its distribution are of considerable diagnostic importance Most typically the lesion is first seen on the forehead and wrists Later it also involves the face and upper extremities and finally it appears on the trunk and lower extremities It is of a centrifugal distribution and tends to involve the exposed parts of the body namely, the face and arms The palms and soles are not spared but the horny character of the epidermis distorts the appearance of the lesion and prevents the development of pustules

One of the most important differential features of the smallpox eruption is the tendency for all the lesions to appear at the same stage of development in a given area of the skin Again in contrast to chickenpox the lesions are said to be *monomorphic* rather than pleomorphic See *Differential Diagnosis of Vesicular and Pustular Eruptions* (p 422)

Constitutional Symptoms —The temperature and constitutional symptoms subside when the eruption appears At the time that the vesicles appear the *temperature* again tends to rise and when the stage of pustulation is reached a *secondary fever* is present This may be quite severe but in mild cases it is frequently absent altogether In any instance the fever disappears completely by the time the pustules begin to dry and form scabs which is usually about the twelfth day Itching may be very marked especially when the pustules are tense with fluid *Pitting* is a common sequel of the confluent types of smallpox but, in the discrete and mild type now prevalent, it is uncommon The lesions of the mucous membranes are quickly macerated and appear as shallow ulcerations They may produce painful stomatitis salivation and changes in voice if they involve the larynx

Enlargement of the spleen liver and superficial lymph nodes is common

Variations —The clinical variations of smallpox carry distinctly different implications as regards prognosis *Hemorrhagic types* in which the vesicles fill with blood are very rare and most malignant In *confluent smallpox* which corresponds to the severe type the lesions are so numerous that they tend to coalesce This type is marked by a stormy course and is followed by disfigurement pitting and scarring The *discrete type* is clinically milder The lesions may be few or many but not so numerous as to coalesce In *this type* of smallpox the secondary fever is often absent

Alastrim —The type of smallpox most commonly seen in the United States today is the so called alastrim ' a mild form of discrete smallpox

practice where debilitated infants are treated They are most uncommon in private practice

A transitory febrile *albuminuria* is not uncommon in measles but the glomerulonephritis of scarlet fever is not observed

In institutional practice measles is often accompanied by other communicable diseases such as *scarlet fever chickenpox* and *diphtheria* These are probably cross infections and are infrequently seen in children who are treated at home

Measles may activate a *pulmonary tuberculosis* Children develop measles at the age of the primary tuberculous infection and the acute exanthematous disorder may so depress the tissue defenses as to permit the tuberculous process to gain rapid headway In children with a positive family history for tuberculosis a chest film should be taken following the attack of measles to estimate the extent of the damage

Diagnosis

The diagnosis of a typical case of measles offers no difficulty Recognition of the Koplik spots precludes any possibility for confusion However if the child is not seen until the enanthem has faded principal reliance is placed upon association of catarrhal symptoms and a profuse maculopapular eruption In contradistinction to the other disturbances such as rubella which produce generalized cutaneous manifestations measles has more severe constitutional manifestations less marked posterior cervical adenopathy and a slower evolution and involution of the eruption The rash of *scarlet fever* is a diffuse punctate erythema which does not involve the face This disease is also characterized by the specific blanching reaction (p 179) and the later appearance of the strawberry tongue The morbilliform eruption of *secondary syphilis* is rarely accompanied by significant fever or marked constitutional symptoms *Drug rashes* rarely produce simultaneous catarrhal symptoms though they may be associated with fever

Laboratory Data —The laboratory examinations in measles are characterized by their normality There is usually a normal or lowered leukocyte count The presence of a leukocytosis suggests bacterial complications

Prognosis

The mortality rate of measles is extremely low in children over the age of three Complications leading to death are most often seen in young infants and in those debilitated youngsters who suffer from some other chronic disease

Treatment

Measles may be temporarily prevented or the expected course may be modified by the injection during the incubation period of substances which contain the measles antibody The preparations in clinical use include human convalescent serum the immune serum or whole blood of adults immune globulin obtained from human placenta and gamma globulin derived from plasma

antibiotics has no striking specific value in the treatment of smallpox. Nevertheless because of the severity of the disease it would seem a wise precaution to employ both *penicillin* and a soluble sulfonamide such as *sulfadiazine* in full therapeutic dosage. If these remedies do nothing else they may prevent or mitigate secondary complications from sensitive or susceptible micro organisms.

VACCINIA (COWPOX)

Edward Jenner's observation in 1798 that inoculation with cowpox protects against smallpox was one of the great discoveries of medicine. Jenner gave the world a method by which smallpox could be entirely eradicated. The early method of vaccination by injecting material from one person into another had certain dangers which gave the anti vaccinationists' fuel for argument. These vocalizations are still heard despite the fact that the preparation of vaccinia virus is entirely different.

The principle of vaccination is the *production of immunity to smallpox by inducing cowpox or vaccinia. Vaccinia is a local mild infection which is followed by durable immunity to smallpox.* The relation of smallpox to cowpox has long aroused interesting speculation. It was assumed that the two viruses were closely related since infection with one (*vaccinia*) resulted in immunity to the other (*variola*). Recent immunological studies confirm that the two viruses are antigenically closely related if not identical. Small pox virus passed through the cow produces cowpox and passage through the cow so modifies the virus that on subsequent injections into humans only cowpox is produced.

VACCINIA

Vaccinia the disease produced by vaccination is manifested by the development of a characteristic lesion at the site of inoculation. There is much evidence that the vaccinia virus gets into the *blood stream* probably first from the regional lymphatics and is distributed to all the tissues. It is considered possible that vaccinia virus produces long lasting immunity because living virus persists in the body in minute foci and serves continually as an antigen. Supporting evidence for this theory is afforded by the fact that inoculation with dead vaccinia virus produces only transitory and ineffective immunity.

Vaccinia is not contagious but one child may inoculate another in intimate contact.

COWPOX VACCINE

At the present time the bulk of vaccine is made in calves. The seed virus is applied to scarified areas of the abdomen and thighs of the animal. After the development of vesicles the material is scraped off and the pulp collected. Extraordinary precautions are taken to prevent bacterial contamination since the material cannot be subjected to sterilization as the virus must be kept in the living state. After final processing the material is almost bacteria free and is carefully tested to insure that tetanus and other pathogenic organisms are absent. The virus must be kept cold as it rapidly deteriorates and loses potency at warm temperatures.

In recent years other methods of producing vaccine v[illegible] have been

SYMPTOMATIC TREATMENT

The generic treatment recommended for the management of all of the infectious diseases is instituted (p 64) Because of the photophobia the room is best kept darkened and the patient should wear smoked or blue glasses Measles is reportable Placarding of the home is usual and susceptible children are quarantined

RUBELLA (GERMAN MEASLES)

German measles is a mild infectious disease with a short prodromal period mild constitutional symptoms and a rash of prominent but variable appearance Its chief importance lies in the fact that it may be confused with measles or scarlet fever Despite the confusing similarity of names German measles is unrelated to measles since an attack of one does not protect against the other Likewise it has no relation to scarlet fever

The etiology of rubella is generally assumed to be a filtrable virus It is highly contagious and usually occurs in epidemic form during the winter and spring months Persons in all age groups past the first six months of life are susceptible Although children are most commonly affected the disease is not rare among adults One attack usually confers immunity

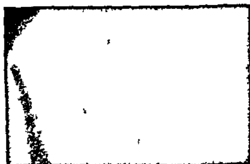


Fig 66—Scarlatiform rash in rubella

CLINICAL MANIFESTATIONS

The *incubation period* of German measles is fourteen to twenty-one days The disease usually begins with mild prodromal symptoms of malaise slight fever and coryza These are present for twelve to twenty four hours before the appearance of the rash At this time an *enanthem* of minute bright red spots may be observed on the uvula and soft palate

The *rash* which may be the first evidence of the disease appears first upon the face and then spreads to the rest of the body The lower extremities are involved last Most frequently the rash is composed of tiny maculopapules which are usually discrete but may be confluent on the face In this form the appearance is suggestive of measles but there may be also a generalized punctate erythema which simulates the eruption of scarlet fever Less than a day is required for the full evolution of the rash which rarely lasts more than three days and then fades in the order of its appearance Desquamation is variable and may be slight or entirely absent When it occurs it is in the form of fine scales

one of the tissue culture virus preparations is available It was hoped that scars could be avoided entirely by this procedure but this goal has not been achieved There is some evidence suggesting that the immunity resulting from tissue culture virus is less lasting than calf lymph inoculation For the present the method of choice is calf lymph virus inoculation by the multiple pressure method

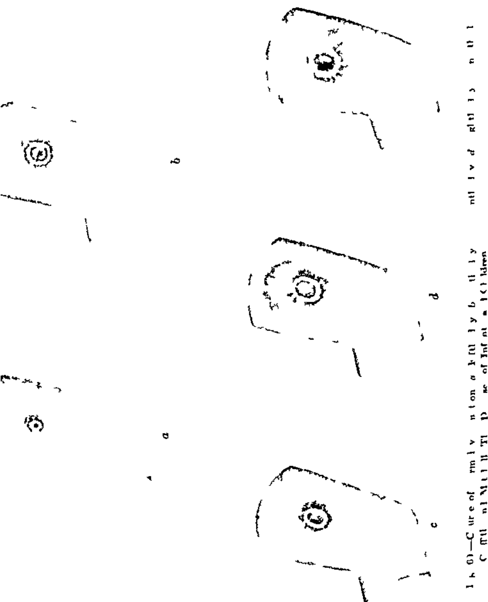


Fig 61 —Course of primary vaccination [illegible]
[illegible] Diseases of Infants and Children

After Care

In the after care of the site of vaccination prevention of bacterial infection is the chief objective Small infants and children must be prevented from scratching Dressings and especially shields that cover the lesion are prohibited since they provide anaerobic conditions favorable for the growth of tetanus If the vesicle ruptures and becomes wet a sterile gauze pad is

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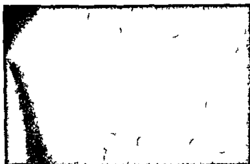


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Primary Take —Following primary vaccination nothing is noticed until the third to sixth day when a small red papule appears Within twenty four hours the papule is converted to a small vesicle which continues to en large reaching its full development on or about the ninth day At this time the lesion may be ¼ inch in diameter and of a pearly gray color Durin the next two days a bright red indurated areola forms about the vesicle From this time on the vesicle begins to dry and form a crust The crust separates in one or two weeks leaving a pink scar which eventually becomes white and somewhat puckered

At the height of the process there may be fever loss of appetite and restlessness The axillary lymph nodes are usually enlarged and somewhat tender The constitutional reaction rarely lasts more than three or four days

Accelerated Reaction —The accelerated reaction is seen in partially im mune persons who have been previously vaccinated It is of shorter dura tion and milder than the primary type of reaction The vesicle reaches its maximum on the fourth to seventh day and then dries up Systemic re action is minimal or absent

Immune Reaction —The immune reaction consists in the appearance of a small papule surrounded by an areola and develops twelve to seventy two hours after vaccination No vesicle forms and the reaction disappears com pletely in four or five days

Duration of Immunity

The duration of immunity is variable but appears to be *at least five years* In the Detroit epidemic no person contracted smallpox who had been vaccinated within five years preceding the epidemic *It is therefore recommended that children vaccinated in the first year of life be revac cinated on entering school* It is probable that the degree of immunity resulting from this repeated vaccination will endure for a very long time Revaccination is required for everyone in the community in which there is a recognized epidemic of smallpox however mild

Contraindications to Vaccination

Vaccination should not be attempted immediately after recovery from measles and certainly not in the incubation period of any systemic disease such as whooping cough chickenpox or measles The presence of infantile eczema does not contraindicate vaccination but if the eruption is severe and generalized it may be preferable to postpone vaccination until the condition of the skin is improved Persons suffering from chronic derma toses should not be vaccinated by the scratch method but by the intra cutaneous method

Complications of Vaccination

Pyogenic infection of the vesicle is the commonest complication This can be prevented by cleanliness and the avoidance of bandages and shields

Postvaccinal tetanus occurs rarely It is probable that tetanus spores are introduced subsequent to the vaccination and are not present in the lymph itself There is usually evidence of an injury to the vesicle in these cases

never seen a case The disease is characterized by an eruption which lasts from six to ten days It is unaccompanied by constitutional symptoms

The etiology and method of transmission of the disease are entirely unknown Children from the ages of two to ten are affected Infants and adults rarely develop the disease

The characteristic and only symptom of erythema infectiosum is the *rash* which first appears symmetrically on the face as large red *macules* that quickly coalesce giving the appearance of a facial erysipelas (p 167) The nasolabial area is not involved The skin is warm and somewhat swollen but does not itch or pain The rash gradually changes from a rose color to a deep cyanotic bluish red Simultaneously the eruption develops over the rest of the body especially the arms and legs It spreads toward the periphery the hands and feet being affected last As the individual lesion progresses the centers of the macules fade and produce a *lacelike appearance* After six to ten days the entire lesion disappears without producing pigmentary changes or desquamation Leukopenia accompanies the disease

The eruption is distinguished from *measles* and *rubella* by its totally different appearance Koplik spots are not observed and there is no lymph adenopathy

See *Differential Diagnosis of Eruptive Fevers* (pp 172 174)

Erythema infectiosum is an entirely benign disease It has no complications and requires no treatment

SIXTH DISEASE (EXANTHEMA SUBITUM ROSEOLA INFANTUM ROSE RASH PSEUDORUBELLA)

Exanthema subitum is an acute disease of infants characterized by a *fever* which lasts for two to five days an absence of localizing signs or symptoms and the appearance of a *morbilliform eruption* that follows the critical fall of temperature

The etiology is presumed to be *viral* although no proof of this has as yet been offered The disease is apparently common though it is so little known that it is probably more often overlooked than properly identified

Exanthema subitum generally occurs sporadically with little evidence of direct transmission Several small epidemics have been reported in pediatric institutions and foundling homes The disease occurs most often in spring and fall and 95 per cent of the afflicted are children under the age of two and one half years It is never fatal and its pathology is unknown

Clinical Manifestations

The *incubation period* of exanthema subitum is ten days but it may vary from eight to forty one days The disease begins abruptly with a *high fever* which lasts from two to five days The temperature is elevated to 103 to 105 F There are morning remissions and an acute fall to normal at the time the eruption makes its appearance Vomiting restlessness and irritability are usually seen Older children may complain of *headache* and in young infants a *convulsion* may occur at the onset Mild respiratory symptoms may be present but more often are entirely absent Some enlargement of the cervical lymph nodes may be seen but the lymphadenopathy is not prominent as it is in German measles The spleen is not palpable and the physical examination otherwise is entirely normal

Generalized vaccinia is a rare complication of vaccination consisting of a more or less widespread eruption of vaccinia lesions resulting from autoinoculation of virus to other parts of the skin It occurs chiefly in persons with chronic skin diseases eczema and other dermatoses Very rarely persons with normal skin develop generalized vaccinia following vaccination with an unusually potent virus This complication is quite serious There is a sharp febrile response and an appreciable mortality that is higher in those with chronic diseases of the skin than in persons with normal skin There is no specific therapy available The most important preventive is to keep recently vaccinated persons away from contact with individuals suffering from chronic dermatoses

Postvaccinal encephalomyelitis the most severe complication of vaccination may be due to vaccinia virus itself to the activation of a previously dormant neurotropic virus or it may be an allergic reaction of the central nervous system to the vaccinia virus Despite a large volume of experimental work the etiology is still not clear but considering the many thousands of vaccinations performed each year this complication is extremely rare

Postvaccinal encephalomyelitis usually develops suddenly from seven to fourteen days after vaccination with headache fever convulsions and paralysis Death may occur in two to four days The symptoms are those of diffuse cerebral involvement The case mortality is 35 per cent or more It has been shown that this complication is most likely to occur during the summer in persons over three years of age and during primary vaccination Hence if primary vaccination is done in infancy in the colder months revaccination can then be done with little fear at school age

MOLLUSCUM CONTAGIOSUM

Molluscum contagiosum is described in detail in the section on Diseases of the Skin (p 3287)

WARTS (VERRUCAE)

The clinical types and treatment of warts are described in the section on Diseases of the Skin (p 3288)

HERPES SIMPLEX (HERPES FEBRILIS COLD SORES)

Herpes simplex is an acute infectious disease characterized by the appearance of groups of superficial vesicles on the mucocutaneous borders of the lips nose genitalia cornea or other parts of the body

Etiology—Herpes simplex is caused by a filtrable virus which can be recovered from the fluid within the vesicles The virus can be propagated in tissue cultures and on the chorio-allantoic membrane of developing chick embryos When injected into the scarified cornea of a rabbit's eye a severe *keratitis* results If the virus is injected intracerebrally into rabbits or mice a fatal *encephalitis* is produced For this reason it was considered possible that von Economo's encephalitis (encephalitis lethargica) (p 441) might be caused by the herpes simplex virus but this hypothesis has been abandoned

Immunity—The virus of herpes simplex is commonly present in man and can be recovered from human saliva even in the absence of any obvious herpetic lesions Following an initial attack of herpes neutralizing antibodies can be demonstrated in the blood of 65 to 90 per cent of adults but they are rarely present in children Despite the presence of antibodies their

Pathology —Chickenpox affects only the superficial layers of the skin and mucous membranes unless secondary bacterial infection develops

Clinical Manifestations

The *incubation period* varies from fourteen to twenty one days The initial pre eruptive symptoms are vague ill defined and of no diagnostic significance They include a gradual onset of malaise headache and moderate fever rarely higher than 101 F that rarely persists for more than one or two days before the development of the rash In children the *prodromes* are milder than in adults and may be entirely overlooked the appearance of the rash being the first evidence of the disease This point is of great help in the differentiation of smallpox which has severe prodromes of longer duration

The Eruption —The rash of varicella appears on the trunk and later involves the head face and extremities It is always most marked on the



F 67—Ch cke pox

trunk and least evident on the exposed parts of the arms and legs It may be present on the palms and soles At first the eruption consists of pinhead pinkish macules which rapidly become papular Within twenty four hours or less these have changed into *vesicles* filled with clear fluid They are surrounded by a small reddish areola which is never more than a quarter of an inch in width The vesicles vary in size and some become quite large In contrast to those seen in smallpox they are very superficial and monolocular Some lack the surrounding areola and appear as drops of water on the skin

In the mildest cases no more than 20 or 30 pocks may be present In the severer manifestations hardly any skin is left uninvolved but no matter how numerous the vesicles of chickenpox never become confluent Within two to four days the individual vesicle has dried up and formed a crust but new crops develop as the first ones disappear The successive

ulcers can be found on the tonsils palate tongue and buccal mucosa *Herpes labialis* may also be present It is not clear whether this represents a primary herpetic infection in an adult or a severe manifestation of recurrent herpes The disease subsides spontaneously within one or two weeks

ENCEPHALITIS AND MENINGO ENCEPHALITIS

Although it has been established on reasonable evidence that epidemic encephalitis lethargica is not caused by herpes simplex virus it has been shown that *this virus may cause encephalitis* There have been a few reported instances in which the virus was recovered from the spinal fluid of patients suffering from an acute non bacterial meningo encephalitis which resembles lymphocytic choriomeningitis (p 448)

TREATMENT

There is no specific treatment for herpes simplex Except when it involves the cornea (p 1626) in cases of herpetic stomatitis and pharyngitis it is ordinarily a benign infection

It is reported that recurrent attacks of herpes can be prevented by repeated vaccination with vaccinia

HERPES ZOSTER (SHINGLES)

Herpes zoster is an acute disease characterized by the appearance of groups of vesicles which follow the distribution of a nerve trunk

Etiology—Herpes zoster is due to a *virus* and human volunteers can be infected by the inoculation with fluid from herpetic vesicles The virus does not produce disease in animals and has not been cultivated in tissue culture Inclusion bodies similar to those present in other virus diseases are found in the cells of the skin lesions

Epidemiology—On epidemiological grounds a relationship between herpes zoster and chickenpox has long been recognized Herpes zoster may appear in a person exposed to chickenpox but more often cases of the latter follow contact with herpes zoster Antigen made from the lesions of either of these diseases will fix complement in the presence of convalescent serum taken from patients with zoster or chickenpox There is therefore an antigenic similarity if not a complete identity between the two viruses

Pathology—The lesions of herpes zoster consist of histological changes in the ganglia of spinal nerves and root fibers Interstitial inflammation and degenerative changes in the nerve cells of the affected ganglia can be demonstrated Regeneration usually takes place but in some instances destruction of nerve cells may be complete These changes are followed by degeneration in the peripheral nerve the posterior nerve root and the corresponding fibers of the spinal cord

The portal of entry of the virus is unknown The virus is probably present in latent form in the human tissues This belief is based chiefly on the observation of so-called symptomatic herpes in which the presence of an irritative lesion near the posterior root ganglia may produce an attack of herpes zoster suggesting that a latent virus has been activated

Clinical Manifestations.—In most instances an attack of zoster develops without obvious cause There is a *prodromal period* of several days with fever malaise and pain in a localized area Diagnosis is difficult or impossible until the eruption appears as groups of vesicles on an erythematous base It is accompanied by *burning* and *itching* and may be quite *painful* The lesions are distributed along the course of a nerve trunk most commonly one of the upper thoracic nerves and follow a segmental distribution Occasionally herpes zoster involves only the branches of the trigeminal nerve and may appear on the face or forehead If the ophthalmic

Sudamen	Multiple non inflammatory crystalline vesicles in febrile or sweaty patients
Syphilis	Secondary eruption may be varicelliform or varioliform (p 338)

crops continue to appear for three or four days even in the same area of the body

The rash is characteristically *pleomorphic* Lesions at all stages of evolution from macules through vesicles to crusts are present at the same time and in the same area This is a point of great importance in diagnosis since in smallpox the lesions in any given area of the body are all in the same stage of development

The vesicles of chickenpox do not become *pustular* unless secondarily infected At times they may appear pustular but if punctured clear fluid appears If undisturbed the crusts drop off in five to twenty days depending on how deeply the skin is involved They leave little or *no scar* unless bacterial infection has occurred The mucous membranes of the mouth are characteristically involved in chickenpox Tiny vesicles form which quickly become macerated leaving superficial ulcerations

Course

The temperature is highest when the eruption is developing most rapidly usually on the second and third day In a case of average severity it does not rise above 101 or 102 F and lasts two days In severe cases it rises a degree higher and persists a day or two longer As the vesicles become crusted the temperature returns to normal Other symptoms such as headache and malaise are mild

Complications

Complications of chickenpox are rare and usually due to secondary bacterial infection causing otitis media pneumonia lymphadenitis cellulitis septicemia or erysipelas *Encephalitis* is a most unusual but serious complication of chickenpox (p 445)

Diagnosis

There is usually no difficulty in the diagnosis of chickenpox especially if a history of exposure can be obtained The chief problem is the differentiation from mild cases of *smallpox* The diagnostic points that favor varicella are the short and mild prodromal period the marked localization of lesions on the trunk the rare involvement of the scalp and the exposed parts of the extremities the presence of the various stages of the lesions at the same time in the same area of the skin the superficial monolocular appearance of the individual vesicle with its clear fluid In contrast smallpox is marked by a more severe and more prolonged prodromal period the pocks are deeper pustular and tend to involve the face and extremities more than the trunk all the pocks in a given area are at the same stage of development at any one time

See also *Differential Diagnosis of Eruptive Fevers* (pp 172 174)

and prevention of secondary infection are the objectives of treatment Painting the lesions with *collodion* is often an effective form of local therapy *Roentgentherapy* is advocated but should be used with caution The best results are obtained when treatment is given early in the course of the disease Relief is sometimes afforded by freezing with an ethyl chloride spray

Ultraviolet light treatment often appears to be quite effective in relieving pain and cutting short the course of the disease Despite enthusiastic statements to the contrary injections of *thiamine chloride* have no therapeutic effect on herpes zoster Subcutaneous or intramuscular injections of *pitressin* have been recommended but are not effective in our experience *Analgesics* and *narcotics* may be necessary for the relief of pain

Post herpetic neuralgia is a distressing condition and very refractory to treatment If the pain is intractable *paravertebral procaine block* or *alcohol injection* may prove palliative

Herpes zoster is considered in greater detail in the section on Dermatology (p 2112)

MILIARY FEVER

Miliary fever is a benign infectious disease of unknown etiology It occurs in epidemics It is characterized by elevation of *temperature* profuse *sweating* profound *prostration* and the appearance of an *erythematous rash* with miliary *vesicles*

So far as is known this disease has not occurred in the United States It has no reported complications of mortality There is no form of specific therapy

FOOT AND MOUTH DISEASE (EPIZOOTIC ECZEMA)

Foot and mouth disease is an acute communicable disease caused by a filtrable virus and transmitted from animals It is characterized by a vesicular eruption of the mouth lips and hands It may attack children or adults and frequently occurs in endemic form

Etiology—Foot and mouth disease is caused by a *filtrable virus* which is present in the tissues of *infected cattle goats sheep and pigs* Other animals as horses cats and dogs also may be infected Transmission may be by drinking *raw milk* or by the ingestion of cheese butter or animal tissue Infections by *inoculation* into wounds of the hands arms or face also occurs There is a high concentration of the virus in the vesicles and the saliva

Clinical Manifestations—The condition usually begins with *fever chilly sensations headache* and *malaise* Soon there appears the typical *vesicular eruption* of the mouth lips hands and less often of the feet The vesicles are clear at first Later they become turbid rupture and give rise to raw eroded surfaces At times vesicles may be present in the pharynx and on the conjunctiva Salivation and cervical lymphadenopathy are frequent concomitants

Course—The course is usually *benign* terminating in recovery in several weeks In sickly undernourished infants and children death may ensue

Diagnosis—In the presence of an endemic there is little difficulty in diagnosis In isolated instances the differentiation from *bullous multiform*

is eradicable by vaccination smallpox continues to be surprisingly prevalent in certain sections of the United States

Etiology—More than fifty years ago Guarnieri described *inclusion bodies* in the affected epithelial cells of the pustules of variola These were considered to be protozoa In 1906 Paschen found that the inclusion bodies contained elementary bodies which were filtrable It is now recognized that the etiological agent is a *filtrable virus* and consists of these visible elementary bodies By ultracentrifugation it has been found possible to measure the size of the elementary bodies of variola and they are among the largest of the known viruses The virus of smallpox obtained from the vesicles can be cultivated on the chorio-allantoic membrane of developing chick embryo

Epidemiology—Smallpox is *worldwide* in distribution and epidemics of great severity were frequent in this country as well as in Europe The widespread use of vaccination has contributed greatly to the decreased incidence of the disease In those states which have compulsory vaccination laws the disease has been almost completely eliminated but it is still common in the middle west and mountain states where the population is largely unvaccinated

The *virulence* of smallpox varies markedly and may be mild or extremely severe The classical and severe type was seen most recently in Detroit in 1924 where there was a case mortality of 10 per cent in a moderately large epidemic The majority of cases however are mild with a mortality of less than 1 per cent To these modified forms numerous names such as *alastrim cottonpox* and *para-smallpox* have been applied but the disease is still essentially variola

Smallpox is characteristically present during the colder winter months and tends to disappear during the summer It is *infectious* and *transmissible* throughout its entire clinical course from the latter part of the incubation period until the crusts have entirely disappeared Transmission is from person to person by droplet infection from discharges of the respiratory tract or by contact with crusts from healing pustules

When smallpox was widely prevalent it chiefly attacked children and adults were immune since they had already had the disease At the present time in this country it is as common in adults as in children This is explained by the fact that there is no natural immunity and all ages are equally susceptible

Immunity—The immunity which follows recovery from smallpox is usually *lifelong* The mechanism of this active immunity is not clearly understood but viruscidal and complement fixing antibodies are demonstrable in the blood of the recovered patient

Acquired immunity also results from vaccination with the virus of cowpox as is described in the next section (p 429)

Pathology—The skin and mucous surfaces are chiefly affected in smallpox but visceral lesions may also be present The mucous membranes involved include those of the upper respiratory passages the pharynx the bronchi and the gastro intestinal tract Cloudy swelling and focal necrosis of liver and spleen produce enlargement of both these organs A general lymphadenopathy is also usually present

CLINICAL MANIFESTATIONS

The *incubation period* varies from eight to fourteen days The *prodromal* or *invasive stage* lasts three or four days and terminates rather abruptly when the skin lesions appear The *onset* is rather sudden with *headache malaise myalgia* and *fever* of 103 to 104 F or higher *Chills* may occur at the onset *Convulsions* and *vomiting* may be initial symptom in children Pain in the back or extremities and headache may be very intense and of the type encountered in severe influenza or dengue fever The symptoms increase in severity as the temperature and pulse rate increase during the first three days In a small percentage of patients transitory *scarlatiniform* or *morbilliform eruptions* appear during the initial febrile stage

See *Differential Diagnosis of Eruptive Fevers* (pp 172 174)

The Eruption —On the third to fifth day after onset the eruption appears

CHAPTER 21

VIRUS INFECTIONS, NEUROTROPIC

Rabies	Lymphocytic Choriomeningitis
Epidemic Encephalitis	Equine Encephalomyelitis
Japanese B Encephalitis	St Louis Encephalitis
Russian Seasonal Encephalitis	Acute Anterior Poliomyelitis
Post Infectious Encephalitis	

RABIES (HYDROPHOBIA)

RABIES is an acute infectious disease of lower animals due to a filtrable virus It is communicable to man and though it is quite rare the universal gravity of the disease gives it an importance greater than its actual incidence might seem to warrant

Etiology.—Rabies is caused by a *neurotropic virus* The disease can be produced in rabbits and mice by intracerebral inoculation of virus It has been grown also in tissue culture

Epidemiology.—Rabies is world wide in distribution but in England and Australia where rigid quarantine laws are enforced it has been eradicated The natural hosts of the virus are many wild and domestic animals including the dog cat, cattle wolf fox and skunk *In the vast majority of cases man is accidentally infected by the bite of a rabid dog*

It is stated that from 50 to 100 human fatalities annually result in America from rabies About 25 per cent of persons actually exposed to rabid animals develop rabies if they do not receive prophylactic treatment The handling of a rabid dog will not result in infection and it is doubtful whether contact of saliva with the unbroken skin will result in infection Certainly if the rabid dog's saliva contaminates clothing infection will not result The ingestion of food or the drinking of milk from a cow which subsequently dies of rabies will not produce the disease in humans These points are emphasized because there is a tendency to give prophylactic vaccination just to play safe

Rabies is transmitted to humans by the actual bite of a rabid animal so that infected saliva is present in the wound Bites about the head and face are most dangerous while those on the extremities are less so Natural immunity to rabies does not appear to exist

Pathology.—Rabies produces an inflammatory reaction in the brain with lymphocytic infiltration about blood vessels particularly in the substantia nigra Ammon's horn and the hippocampus major Here are found the pathognomonic *Negri bodies* which are intracellular inclusion bodies in the nerve cells

CLINICAL MANIFESTATIONS

In humans the *incubation period* of rabies varies from two to nine weeks or longer This long incubation period allows time for prophylactic vaccination The incubation period is said to be shorter when the infected wound is on the face or head In dogs the incubation period is from two to eight weeks

The clinical picture is characterized by *progressive involvement of the nervous system* with *muscle spasms* followed by *paralysis coma* and *death* The first evidence of the disease is the development of *irritability* and *difficulty in swallowing* This passes into a stage of *excitement* with extreme *hyperesthesia* and short painful *muscle spasms* These involve particularly the pharyngeal muscles of swallowing Spasms may be initiated by loud noise or the sight of food or water hence the name of *hydrophobia*

The eruption may be abortive and not develop into the pustular stage at all It may progress through the vesicular stage and then regress with crusts forming as the vesicles dry up There may be no more than half a dozen scattered lesions on the face and arms Cases of this type may prove extremely difficult to diagnose

Varioloid —In persons who have been previously vaccinated but whose immunity has been partly lost infection with smallpox results in an abortive attack (varioloid) which is clinically similar to alastrim

Laboratory Data

Although the diagnosis of smallpox is essentially a clinical exercise laboratory procedures have some slight diagnostic value where they are available The *Paul test* requires the application of material obtained by puncturing a pustule to a portion of the scarified cornea of the rabbit In the presence of smallpox tiny vesicles develop and the epithelial cells are found to contain inclusion bodies A *complement fixation test* is also available in specially organized laboratories but appears to have only limited practical value in diagnosis

Complications

The complications of smallpox are chiefly the result of *secondary bacterial infections* of the skin and mucous membranes Furuncles cellulitis and erysipelas may occur Pneumonia and otitis media are occasionally encountered

Diagnosis

The chief diagnostic problem in smallpox is differentiation from *chickenpox* The distinguishing characteristic of the eruption in these two diseases have been previously discussed (p 423) *Secondary syphilis* may also occur in a pustular form The absence of prodromal symptoms and the finding of positive serological reactions readily solve this problem

Prognosis

The mortality of smallpox varies greatly from one epidemic to another In former times the mortality was a high as 25 or 30 per cent In 1924 an epidemic of smallpox in Detroit resulted in a mortality of 10 per cent The usual type of mild discrete smallpox seen in the United States today has a mortality of not more than 1 per cent

Prevention

Active immunization against smallpox by inoculation with the virus of cowpox (*vaccination*) is a highly successful preventive measure If a contact is vaccinated immediately after exposure it is possible to prevent the development of the disease since immunity develops within eight days while the incubation period is eight to fourteen days Vaccination is discussed in detail in the subsequent section (p 429)

Treatment

There is no specific therapy for smallpox Vaccination is of no value once the disease has developed The use of the anti infective agents and

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developed These include cultivation of the virus in tissue cultures and on the chorio-allantoic membranes of developing chick embryos The advantage of these types of preparation is the freedom from bacterial contamination so that they can be injected subcutaneously or intracutaneously

VACCINATION

The most favorable time for primary vaccination is about six month of age Younger infants are more likely to resist successful vaccination At six to nine months infants stand vaccination very well There is little constitutional reaction and it is easier to keep these children clean so as to prevent bacterial infection of the lesion If primary vaccination is delayed until school age the danger of postvaccinal encephalitis is considerably enhanced but revaccination at school age results in an accelerated take with almost no systemic reaction The consensus of opinion favors primary vaccination at the age of six months and revaccination at the time the child enters school

The preferred site for vaccination is the skin of the upper arm over the deltoid muscle This area is less accessible to secondary infection due to scratching and the resulting scar tends to be smaller Some years ago it was fashionable to vaccinate girls on the thigh in order to avoid unsightly scars on the arms This procedure is no longer recommended since the resulting scar is usually much larger and reactions are more severe

The colder months of the year are to be preferred in choosing the time for vaccination since vaccinal encephalitis apparently occurs only in the summer months Moreover vaccina virus is susceptible to heat and vaccination is more likely to result in failure in the summer months

Vaccination may be accomplished by *multiple puncture scratch* or *intracutaneous inoculation* Of these the multiple puncture method is universally recommended as the technic of choice The reaction is less severe the resulting scar is small and the danger of bacterial infection particularly tetanus is minimal

Multiple Puncture—To perform multiple puncture vaccination the skin is gently but thoroughly cleaned with alcohol or acetone preferably the latter After the skin has dried a drop of lymph is expelled on the cleansed area of the skin With the skin held taut a new sterile needle is held almost parallel to the surface of the arm and its tip is pressed up and down about ten times through the virus It is not necessary nor is it proper to draw blood in the procedure and the area of inoculation should not exceed ⅛ inch in diameter As soon as the inoculation is completed the excess lymph is removed with sterile gauze

Scratch Method—With the scratch method the skin is cleansed and a drop of lymph applied With the point of a sterile needle the operator makes a single superficial scratch about ⅛ inch long With the side of the needle the lymph is rubbed into the scratch mark and the excess lymph is wiped off There is no need to make more than one scratch Cross hatched scratches formerly practised should be avoided Severe reactions and large unsightly scars are more apt to follow this than the multiple pressure method There is no relation between the size of the inoculation scar and the effectiveness or duration of the resultant immunity

Intradermal Method—The intradermal method of inoculation is used if

clinical evidences of rabies at the end of ten days To be absolutely certain the animal may be sacrificed at the end of this time and the brain examined Then if there are neither clinical nor laboratory evidences of hydrophobia the discomfort of treatment may safely be avoided

There is no question as to the value of *active immunization* against rabies Less than 1 per cent of persons definitely exposed to rabies and subsequently immunized have developed the disease whereas 25 per cent of persons so exposed can expect to develop rabies if they go untreated

EPIDEMIC ENCEPHALITIS (ENCEPHALITIS LETHARGICA SLEEPING SICKNESS VON ECONOMO'S DISEASE)

Epidemic encephalitis was first clearly described by von Economo in Vienna in 1917 but the disease had been seen in Europe at least two years before In the years that followed from 1917 to 1925 lethargic encephalitis was seen throughout the world and many thousands of patients were affected In the United States it was first recognized in 1918 and peaks of incidence occurred in 1920 and 1924 Since 1926 it has not occurred in epidemic form Although sporadic cases of encephalitis of unknown etiology still occur not many cases have since occurred which resemble the clinical types of encephalitis seen during the period from 1916 to 1925

Etiology—The etiology of encephalitis lethargica has never been established but it is the consensus of opinion that it is due to a *filtrable virus* Considerable speculation centered about the possibility that the virus of herpes simplex might produce this disease but the evidence is inconclusive The serums of patients who recover from epidemic encephalitis do not neutralize any of the known encephalitis viruses

Largely because influenza and encephalitis were epidemic at the same time (1917–1919) a direct relationship between the two diseases was considered but epidemiological study does not substantiate this hypothesis There may be some indirect relationship by which an attack of influenza renders the patient more susceptible to encephalitis

Epidemiology—All ages and both sexes are affected but *young adults* were most commonly stricken In this respect, von Economo's disease differs from poliomyelitis which affects children predominantly and St. Louis encephalitis which chiefly affects older individuals Multiple cases in a single family are rare and there is little or no evidence of direct person to person infection although it was recognized that the incidence of the disease was high in physicians The virus was thought to enter through the nasopharynx but there was no direct evidence for this The disease occurred primarily in the colder months of the year differing sharply in this respect from poliomyelitis St Louis and equine encephalomyelitis

Pathology—The pathology of encephalitis lethargica is not distinctive The meninges show areas of hyperemia engorgement of vessels edema and slight thickening The essential histological feature is perivascular infiltration or cuffing with small mononuclear and plasma cells Sometimes minute hemorrhages are found There is also scattered degeneration of nerve cells with neuronophagia While no part of the brain is spared the microscopic lesions exhibit a predilection for the basal ganglia particularly the substantia nigra and for the midbrain especially the oculomotor nuclei and the tegmentum of the pons

CLINICAL MANIFESTATIONS

Epidemic encephalitis is notable for the *multiplicity of its neurological manifestations* suggesting disseminated and widespread foci throughout the neuraxis Although one sign or symptom often predominates evidence of involvement of multiple areas of the brain is always found The disease is marked by moderate or low grade fever but hyperpyrexia is seen in some rapidly fatal cases The white blood count is not remarkable The

attached to the inner side of the clothing in contact with the lesion but if possible the lesion should be left exposed to the air

POSTVACCINAL RESPONSES

Vaccination with a potent virus may produce a *primary take* indicating vaccination an *accelerated reaction* indicating partial immunity as

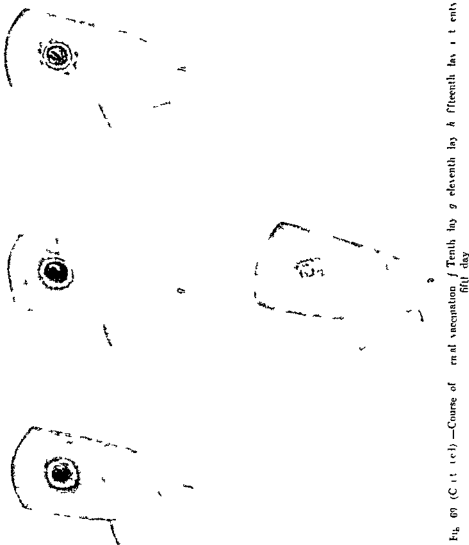


FIG 69 (Continued) —Course of normal vaccination *f* Tenth day *g* eleventh day *h* fifteenth day *i* twenty fifth day

a result of previous vaccination or an *immune response* indicating complete immunity as the result of recent previous vaccination or an attack of smallpox If there is no reaction at all following inoculation it does not indicate immunity but rather failure of technic The commonest cause of failure is impotent or dead virus In such cases vaccination is repeated with *potent vaccine*

Lymphocytic Choriomeningitis	Any	Any	Slightly Turbid	100 to 1000	Small Mononuclears	+	+	Benign course Sporadic
Equine Encephalomyelitis East	Late Summer	Children	Slightly Turbid	50 to 2000	Polymorphonuclears	+	+	High mortality in epidemics
West	Late Summer	Adults	Slightly Turbid	50 to 2000	Polymorphonuclears	+	+	High mortality in epidemics
St. Louis Encephalitis	Late Summer	Adults	Clear	50 to 500	Mononuclears	+	+	Moderate mortality in epidemics
Acute Ant Poliomyelitis	Summer Fall	Children	Clear	0 to 2000	Polymorphonuclears then Mononuclears	+	+	Epidemic form with peripheral or bulbar paralysis
Tuberculous Meningitis	Any	Children	Clear	50 to [illegible]000	Lymphocytes Reduction in sugar content	—	—	Acid fast bacilli by spread or guinea pig
Syphilitic Meningitis	Any	Adults	Clear	100 to 5000	Lymphocytes	—	—	Serologic tests positive Therapeutic test
Brucellosis Meningitis	Any	Adults	Clear	100 to 5000	Lymphocytes	—	—	Skin test positive Positive cultures
Torulosis	Any	Any	Clear	100 to 500	Mononuclears	—	—	Organism seen in spreads
Toxoplasmosis	Any	Infants	Clear	—	—	—	—	Complement fixation.

Primary Take —Following primary vaccination nothing is noticed until the third to sixth day when a small red papule appears Within twenty four hours the papule is converted to a small vesicle which continues to en large reaching its full development on or about the ninth day At this time the lesion may be ¼ inch in diameter and of a pearly gray color During the next two days a bright red indurated areola forms about the vesicle From this time on the vesicle begins to dry and form a crust The crust separates in one or two weeks leaving a pink scar which eventually becomes white and somewhat puckered

At the height of the process there may be fever loss of appetite and restlessness The axillary lymph nodes are usually enlarged and somewhat tender The constitutional reaction rarely lasts more than three or four days

Accelerated Reaction —The accelerated reaction is seen in partially im mune persons who have been previously vaccinated It is of shorter dura tion and milder than the primary type of reaction The vesicle reaches its maximum on the fourth to seventh day and then dries up Systemic re action is minimal or absent

Immune Reaction —The immune reaction consists in the appearance of a small papule surrounded by an areola and develops twelve to seventy two hours after vaccination No vesicle forms and the reaction disappears com pletely in four or five days

Duration of Immunity

The duration of immunity is variable but appears to be *at least five years* In the Detroit epidemic no person contracted smallpox who had been vaccinated within five years preceding the epidemic *It is therefore recommended that children vaccinated in the first year of life be revac cinated on entering school* It is probable that the degree of immunity resulting from this repeated vaccination will endure for a very long time Revaccination is required for everyone in the community in which there is a recognized epidemic of smallpox however mild

Contraindications to Vaccination

Vaccination should not be attempted immediately after recovery from measles and certainly not in the incubation period of any systemic disease such as whooping cough chickenpox or measles The presence of infantile eczema does not contraindicate vaccination but if the eruption is severe and generalized it may be preferable to postpone vaccination until the condition of the skin is improved Persons suffering from chronic derma toses should not be vaccinated by the scratch method but by the intra cutaneous method

Complications of Vaccination

Pyogenic infection of the vesicle is the commonest complication This can be prevented by cleanliness and the avoidance of bandages and shields

Postvaccinal tetanus occurs rarely It is probable that tetanus spores are introduced subsequent to the vaccination and are not present in the lymph itself There is usually evidence of an injury to the vesicle in these cases

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thecally Only after there is definitive evidence of the worthlessness of these *remedies should active therapy* be *discontinued* The treatment of the paralysis agitans and other postencephalitic syndromes is discussed elsewhere (p 1506)

JAPANESE B ENCEPHALITIS (RUSSIAN AUTUMN AND AUSTRALIAN X DISEASES)

Japanese B encephalitis has been recognized as a clinical entity for many years occurring in epidemic form Clinically and in its seasonal prevalence it resembles the St Louis type of encephalitis As far as is known it is limited to Japan among *rice workers* who are continuously exposed to mosquitoes It is thought to be *mosquito borne* A vaccine prepared from formalized infected mouse brain is available

See *Differential Diagnosis of Nonsuppurative Meningomyelomeningitides* (p 442)

RUSSIAN FOREST SPRING DISEASE (LOUPING ILL)

Russian seasonal encephalitis is another type of encephalitis in which the causative *virus* is known It occurs exclusively in the early spring and disappears in the summer It is transmitted by *ticks* and occurs in forests and wooded areas because of the distribution of the vector Recovered cases develop permanent immunity and have *neutralizing antibodies* in their blood A *formalized vaccine* is now being used for active immunization in Russia and appears to be very efficacious

See *Differential Diagnosis of Nonsuppurative Meningomyelomeningitides* (p 442)

POSTINFECTIOUS AND POSTVACCINAL ENCEPHALITIS

Encephalopathies may rarely follow measles chicken pox smallpox influenza B lymphogranuloma venereum herpes simplex anti rabies treatment vaccination and various bacterial infections There is no agreement as to their etiology According to one view these forms of encephalitis are due to a latent virus that is activated by the acute disease An analogy to this hypothetical condition is to be found in the case of the herpes simplex virus which appears to remain latent in the tissues becoming activated and producing lesions as a result of many nonspecific stimuli (p 434) The fact that similar clinical and pathological types of encephalitis follow such different predisposing causes lends support to this hypothesis In contrast to this unitarian view other investigators believe that each form of encephalitis is due to the virus of the acute infection which it follows or accompanies Only in the case of mumps is there any considerable support for this view Finally observations by Dr Thomas Rivers suggest that encephalitis represents an allergic reaction Animal experiments indicate that the skin which is derived from the same embryonic layer as the nervous tissue becomes altered as a result of the localization of the various viruses and becomes antigenic for nervous tissue resulting in the perivascular demyelinization seen in these types of encephalitis

See *Differential Diagnosis of Nonsuppurative Meningomyelomeningitides* (p 442)

is no permanent immunity to herpes and recurrent attacks are very frequent It seems likely that a recurrent attack of herpes represents a reactivation of a virus which has remained dormant in the tissues In the presence of a nonspecific febrile reaction or other physiological disturbance the virus becomes activated and produces characteristic fever sores

Pathogenesis—Herpes febrilis commonly develops in association with pneumococcus pneumonia, meningococcemia cerebrospinal meningitis malaria and other diseases which are characterized by fever Foreign protein therapy vaccine injections and even the menstrual period may precipitate an attack of herpes

Clinical Manifestations

The virus of herpes simplex may produce the characteristic vesicles of the skin and mucous surfaces aphthous stomatitis and gingivostomatitis herpetic pharyngitis and stomatitis and occasional involvement of the central nervous system (p 445)

The lesions of herpes simplex may occur anywhere on the body including the *genitalia* (herpes genitalis) but are most commonly seen on the *lips* There is at first a painful erythema on which a group of superficial *vesicles* quickly develops After a few days they dry with the formation of *crusts* It is doubtful if herpes simplex itself commonly produces any systemic symptoms Since it usually occurs in the presence of a febrile disease the symptoms of herpes itself are likely to be masked by the primary disease The affected epithelial cells contain characteristic inclusion bodies in which the virus particles are present See Fig 70 p 388

Aphthous Stomatitis and Gingivostomatitis

Aphthous stomatitis and gingivostomatitis in children represent primary infections with the virus of herpes simplex Following recovery from this infection *virus neutralizing antibodies* develop although the virus may persist in the normal tissues of the mouth indefinitely and produce recurrent attacks of stomatitis or herpes febrilis

Unlike the recurrences of the infection which are largely asymptomatic the *primary infection* is accompanied by considerable constitutional reactions There is a gradual onset of fever irritability and sore mouth with an elevation of temperature from 99° to 105° F lasting two or three days Swelling of the submaxillary lymph nodes is present The gums are swollen and red Sometimes they almost cover the teeth and bleed easily Small pinhead vesicles develop and soon rupture leaving round or irregularly ovoid yellowish white superficial *ulcers* with a surrounding red halo The tongue gums and buccal mucosa are involved principally but the fauces tonsils and pharynx may also be affected Oral fetor is present in all cases The disease lasts about ten days

Local treatment with gentian violet potassium permanganate or various antiseptic lotions is of doubtful value Although fusospirochetes are commonly present they are not considered to be the causative agent

Herpetic Pharyngitis and Stomatitis (Herpetic Fever)

Herpetic pharyngitis and stomatitis are sometimes seen in adults The disease which is known as Herpetic Fever is rarely recognized although it is probably not uncommon It is characterized by fever malaise headache and sore throat Tiny vesicles which quickly rupture to leave shallow

of the cases and shortly after it was completed in the remainder Three clinical types have been described (1) Sudden onset with fever head ache vomiting backache insomnia and restlessness followed by paralysis of the legs and sphincters This resembled an ascending or Landry type with death resulting from bulbar paralysis (2) a more gradual onset of weakness or paralysis with anesthesia of the arms or legs (3) neuritic forms in which the peripheral nerves most often the facial are involved

Complete recovery is the rule in the last type and may be partial or complete in the others

Mumps Meningoencephalitis

See p 483

Pertussis Encephalopathy

Convulsions are fairly common in whooping cough but it is difficult to consider the diagnosis of encephalitis or encephalopathy unless they are frequent and severe or accompanied by other evidence of nervous involve ment In an extremely small number of patients convulsions somnolence stupor apathy or coma may develop suddenly one to five weeks after the onset of the cough These are accompanied by a variety of objective neurological signs

The course is extremely variable About 25 per cent of the patients die during the acute stages more than half recover and the remainder are left with evidences of chronic damage to the central nervous system

Encephalitis Following Bacterial Infections

Delirium stupor convulsions and other nervous symptoms may de velop on rare occasions during the course of many infectious diseases such as scarlet fever tonsillitis erysipelas pneumonia dysentery and other bacterial infections Similar symptoms are more commonly produced by actual meningeal or brain involvement by infection secondary to bac teremia or to middle ear infection

These may be regarded as evidences of encephalitis or as a toxic en cephalopathy The spinal fluid is bacteriologically sterile and usually shows a slightly increased protein content and cell count

Meningismus is fairly common in children at the onset of pneumonia In such patients the symptoms are transitory and the spinal fluid findings normal

The prognosis of acute toxic encephalopathy secondary to bacterial infections is usually good most patients recovering completely In a small number of patients permanent damage to the brain results

Treatment

The treatment of all forms of encephalitis and encephalopathy is purely symptomatic Lumbar puncture is done as an aid to diagnosis and may be helpful for the relief of headache and other symptoms of increased intracranial pressure In the management of such patients the chief prob lems are the maintenance of nutrition the control of restlessness and the prevention of pneumonia and decubitus ulcers

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Clinical Manifestations

The virus of herpes simplex may produce the characteristic vesicles of the skin and mucous surfaces aphthous stomatitis and gingivostomatitis herpetic pharyngitis and stomatitis and occasional involvement of the central nervous system (p 445)

The lesions of herpes simplex may occur anywhere on the body including the *genitalia* (herpes genitalis) but are most commonly seen on the *lips* There is at first a painful erythema on which a group of superficial *vesicles* quickly develops After a few days they dry with the formation of crusts It is doubtful if herpes simplex itself commonly produces any systemic symptoms Since it usually occurs in the presence of a febrile disease the symptoms of herpes itself are likely to be masked by the primary disease The affected epithelial cells contain characteristic inclusion bodies in which the virus particles are present See Fig 70 p 388

Aphthous Stomatitis and Gingivostomatitis

Aphthous stomatitis and gingivostomatitis in children represent primary infections with the virus of herpes simplex Following recovery from this infection *virus neutralizing antibodies* develop although the virus may persist in the normal tissues of the mouth indefinitely and produce recurrent attacks of stomatitis or herpes febrilis

Unlike the recurrences of the infection which are largely asymptomatic the *primary infection* is accompanied by considerable constitutional reactions There is a gradual onset of fever irritability and sore mouth with an elevation of temperature from 99° to 105° F lasting two or three days Swelling of the submaxillary lymph nodes is present The gums are *swollen and red Sometimes they almost cover the teeth and bleed easily* Small pinhead vesicles develop and soon rupture leaving round or irregularly ovoid yellowish white superficial *ulcers* with a surrounding red halo The tongue gums and buccal mucosa are involved principally but the fauces tonsils and pharynx may also be affected Oral fetor is present in all cases The disease lasts about ten days

Local treatment with gentian violet potassium permanganate or various antiseptic lotions is of doubtful value Although fusospirochetes are commonly present they are not considered to be the causative agent

Herpetic Pharyngitis and Stomatitis (Herpetic Fever)

Herpetic pharyngitis and stomatitis are sometimes seen in adults The disease which is known as Herpetic Fever is rarely recognized although it is probably not uncommon It is characterized by fever malaise headache and sore throat Tiny vesicles which quickly rupture to leave shallow

There is usually little evidence of focal involvement of the brain The *Babinski signs* may be positive and there is often transient weakness of different muscle groups but frank localizing neurological signs are uncommon There is generally a moderate *leukocytosis* with a normal differential count The *spinal fluid* is under moderately increased pressure and is either clear or ground glass There are generally from 100 to 1000 cells per cu mm 75 per cent or more of which are small mononuclears The protein is increased the sugar and chloride contents normal and the fluid is bacteriologically sterile

The *temperature* remains moderately *elevated for a number of days* and then gradual improvement occurs It may be two weeks or more before there is complete symptomatic recovery and it takes longer for spinal fluid changes to return to normal

The disease is quite *benign* and the case fatality is nil as far as is known A few patients have had residual damage to the nervous system in the form of chronic arachnoiditis and facial paralysis

Encephalitis —A second form of the disease is that of a mild or severe encephalitis and several fatal cases of this type have been described Mild infections may be characterized by drowsiness headache anorexia chilliness and malaise Signs of meningeal involvement are minimal Drowsiness and irritability are the chief evidences of encephalitic involvement but there may be transitory objective neurological signs These patients make a complete recovery in most instances

The fatal examples of this type of disease have usually had a fairly rapid onset of drowsiness progressing to stupor and finally coma Objective neurological signs of widespread brain involvement are evident Hyperpyrexia occurs in most of the fatal cases and leukocytosis is generally marked The spinal fluid is clear with a protein content that is only moderately elevated and a cell count which may be normal or elevated but tends to be lower than in those patients whose disease produces predominantly meningeal signs

Grippe Like Infection —A third clinical type of infection with the choriomeningitis virus is a grippe like or influenzal type of infection The symptoms are a gradual or acute onset of malaise headache pains in the muscles of the extremities or back and arthralgia Moderate fever accompanies the di ease which is self limited and lasts about a week A transitory macular erythema and a superficial grayish ulceration of the mucous membranes of the mouth have been described in a few cases Stiff neck is not present and there are no indications for performing a lumbar puncture

The diagno is has been made only when specific tests for the detection of virus or antibodies were carried out It is obvious that this clinical state is ill-defined and may be produced by many different infectious agents There is at present no knowledge of how frequently illness of this type is due to choriomeningitis or conversely what proportion of choriomeningitis infections are of this type Armstrong in a study of 2000 human serums collected at random found 11 per cent had neutralizing antibodies for the choriomeningitis virus Very few of these persons give a history suggesting central nervous system disease It is therefore possible that a portion of the illnesses ordinarily called grippe or influenza

branch is involved vesicles may develop on the cornea This is a serious complication and may lead to permanent corneal opacities (p 435)

The febrile reaction lasts three or four days and then subsides as the vesicles dry up and heal *Post-herpetic neuralgia* may persist for long periods especially in old people See Fig 70

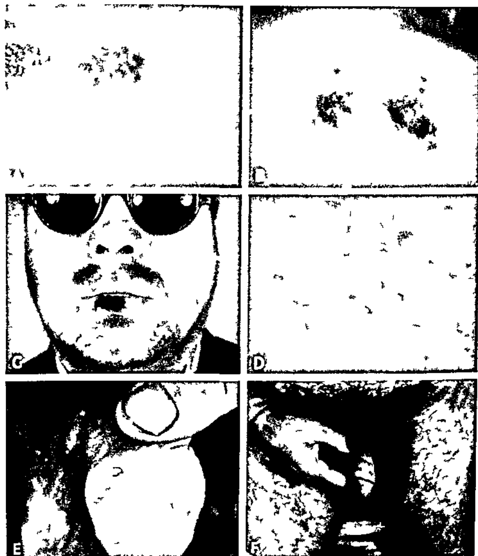


Fig 0—Herpetiform lesions A Herpes zoster of shoulder in vesicular stage *B* Herpes zoster of shoulder in gangrenous stage *C* Herpes simplex of lip *D* Molluscum contagiosum generalized *E* Molluscum contagiosum of glans penis *F* Herpes simplex of penis suggesting venereal lesion

Diagnosis—The diagnosis of herpes zoster is generally obvious once the vesicles appear In the pre eruptive stage the segmental distribution of severe pain accompanied by hyperalgesia may be suggestive

Treatment—There is no specific treatment for zoster Alleviation of pain

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erythema and *pemphigus vulgaris* may require some thought and observation

Treatment—Because of the soreness of the mouth feeding may be a problem Liquid high calory foods are given and when this is difficult *intravenous dextrose solution is advisable* The mouth may be cleansed with an irrigation or gargle of 5 per cent sodium perborate solution The best local therapy is the application of a 2 per cent aqueous solution of *methyl violet* The skin lesions should be protected with a bland ointment

or papilledema the careful removal of spinal fluid under pressure may afford symptomatic relief The principles involving the use of anti infec tive agents are delineated in the material on acute encephalitis

EQUINE ENCEPHALOMYELITIS

Equine encephalitis has occurred in widespread epizootics in this coun try and Canada Although it had been suspected that certain cases of human encephalitis might be due to the same agent the first evidence appeared in 1938 In that year there were a number of small outbreaks of human acute encephalitis in man in the widely separated areas of Massachusetts California North Dakota Minnesota and Saskatchewan Yearly the prevalence and geographical distribution of human infection with equine encephalomyelitis has increased In 1941 more than 3000 cases of this disease were reported in Minnesota North Dakota Man itoba and Saskatchewan *Not since the lethargic encephalitis epidemic of* twenty years before had acute epidemic encephalitis reached such propor *tions From what is known of the distribution of the infectious agents in* animal hosts and its probable mode of transmission it is reasonable to expect that equine encephalomyelitis will become increasingly more prev alent throughout the United States and Canada

Et logy—Equine encephalomyelitis is caused by several closely related *filtrable viruses* In th s country ea tern and western type strai s have been isolated Until recently there has been a curious! sl arp distinction in the prevalence *of the two strains* the eastern type being found east of tl e Appalachian mounta ns and the western type throughout the middle and far west and in the eastern part of Canada Now howe er there is ev dence tl at this strict geographical separat on is breaking down since the western strain has been isol ted in ck horses in Alabama and the eastern strain has been found in Texas The clinical disease in horses is similar with both strains

In addition to man and the hor e guinea p gs m ce rats monkeys rabb ts p geons and many species of wild birds are susceptible to experimental infection with the virus of eastern and western equine encephalomyelitis The infectious a ent can be grown in tissue culture and on the chorio allanto c membranes of f rtile hens eggs The v rus is of relatively small *p rt cle size and is readily destroyed by acid but remains viable for long per ods at cold* temperatures

In patients infected w th the western strain virus has been ecovered from the peripheral blood the spinal fluid and the b ain of fatal cases while the eastern stra n has been recovered only from tl e brain ti sue in fatal infections

Ep demiology—Equine encephalomyelitis ep dem cs occur only in the summer and autumn In this respect the disease re-embles St Louis encephalitis and poliomyelitis but d ffers sharply from lethargic encephal t s

The eastern and western types of tl e disease differ in their case fatal ty rates and the age and sex di tribution of pat nts The case fatality rate of the Massachusetts epidemic (eastern type) *was nearly 0 per cent but in contrast among 3000 cases of the western type* n 1941 the ove all mortal ty rate was 12 4 per cent

The *eastern type of di ease* attacks infants and young children predomi ately with 70 per cent of the ca es being under ten years of age In Califo n a *the western type* also affected children to a large e tent since 50 per cent of the pat ents were less than ten years old On the other hand in the la e 1941 epidemic of western equ ne encepl alomyel tis the great major ty of patients were adults With the eastern type the attack rates were equal for *the two sexes* but with the western type there has been a consistently higher attack rate for males than for females

Equine encephalomyel tis appears to affect chiefly *ru al a d subu ba dw lle s* The e is a complete lack of evidence sugge ting person to person communicability Multiple cases in fam lies are unu ual and when they do occur they are generally simultaneous rather than in succe s on

After several days of tonic and clonic muscle spasms *paralysis* sets in and death results from *respiratory or cardiac failure*

Diagnosis

The diagnosis of rabies is generally evident when the history of a bite and the incubation period are considered Tetanus has a much shorter incubation period and presents a different clinical picture

See *Differential Diagnosis of Nonsuppurative Encephalomyelomeningitides* (p 442)

Prevention

A dog bite wound should be washed thoroughly treated with concentrated nitric acid and allowed to remain open The dog should be caught and locked up under the observation of a veterinarian If he appears normal and remains so for ten days rabies is ruled out in the animal and the patient does not require immunization

If the animal dies the head should be removed packed in ice and sent immediately to the laboratory for examination for Negri bodies and for animal inoculation If these are positive *immunization* must be started immediately Difficulties arise in cases where the dog cannot be located after biting If there is any reason to think it may have been rabid, immunization must be carried out

Pasteur's original vaccine consisted of suspensions of infected rabbit spinal cord in which the virus was attenuated by drying Numerous modifications of the original method have since been devised and the various vaccines vary widely in potency *Semple vaccine* which is a phenolized brain suspension and the *Kelser vaccine* a chloroform treated brain suspension are widely used Recently Webster has developed an ultraviolet light inactivated brain suspension which appears to have many advantages but has not yet received wide clinical trial

The *Semple vaccine* is given by daily subcutaneous injections for a period of fifteen days Each dose is 2 cc Local reactions are usually mild but a small percentage of persons who are vaccinated develop *treatment paralysis* or *vaccinal encephalitis* (p 445) Most of these cases resulted from the early vaccines which contained living virus Since the use of killed virus the incidence of this complication is so small that it should not deter the physician from using vaccine when it is clearly indicated

Treatment should be instituted without delay under any of the following circumstances

1 The person who has been bitten is in a community where rabies is known to be present
2 The patient was bitten the animal apprehended and clinical signs of rabies were noted
3 The animal at autopsy was found to have a brain with positive evidences of rabies
4 The animal was autopsied and although the brain was negative the clinical diagnosis of rabies was suspected
5 The bite occurred about the head and neck

Rabies vaccine need not be given if the bite was on the trunk or extremity and the dog was kept under observation and found free from

enormous variation in the severity of the disease in different patients a common pattern was recognized in most In cases of moderate severity *headache* was the initial symptom Soon after *deep aching pain was felt in the neck and spine* and increasing *mental torpor* developed The patient often continued at work for several days despite severe headache drowsiness abnormal sweating chilliness vomiting anorexia and constipation When finally forced to bed the headache and backache remained and in addition mild or marked disorientation somnolence and nocturnal restlessness or delirium were noted

The general appearance was quite characteristic There were *congestion of the conjunctivae puffiness about the eyes and a coarse plethoric appearance of the face which together with mental confusion dysarthria tremors and drowsiness suggested a delirium tremens* Physical signs were surprisingly scanty and variable and were curiously like those of multiple sclerosis *Nystagmus intention tremor* of the tongue and hands *absent abdominal reflexes* and a *positive Babinski sign* were fairly frequent True signs of meningeal irritation were also uncommon The average temperature was 102° F on the second day and was normal by the tenth day Often symptoms persisted for a few days after the patient was afebrile The pulse rate was relatively slow rarely above 100 per minute

Sequels

In the few patients who recovered from the eastern type of the disease sequels were severe and frequent They included *mental retardation paralysis hemiparesis aphasia* and *emotional instability Residual spastic paralysis* was noted following attacks of the western type of disease in children but the great majority of adults stricken with the western variety of equine encephalomyelitis appear to have made a complete spontaneous recovery Subjective symptoms persisted for some months These included persistent *headache generalized weakness nervousness* and *amnesia* for the preceding acute illness A few had objective findings of *tremor of the hands tongue* or *lips* and *nystagmus Definite paresis* was rare Insufficient time has elapsed to be certain that late sequels such as Parkinsonism will not develop

Diagnosis

In both varieties of the disease the *spinal fluid* is under increased pressure and is clear hazy or of ground glass appearance but is not grossly turbid The *globulin content* is elevated but the *sugar concentration* is *normal* The *cell count* varies from 50 to 2000 cells per cu mm in the first day or two of the disease it consists predominantly of *polymorphonuclear leukocytes* but after several days the *small mononuclear cells* increase both relatively and in absolute numbers *Leukocytosis* of from 10 to 20 000 per cu mm is generally found

On clinical grounds it is difficult if not impossible to make an etiological diagnosis of equine encephalomyelitis except during a recognized epidemic *St Louis encephalitis lymphocytic choriomeningitis* and *poliomyelitis* very closely resemble this disease Epidemics of poliomyelitis and equine encephalitis have occurred simultaneously and in many instances the clinical differentiation has been impossible In poliomyelitis stiff neck

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occurred in St Louis in 1937 and since then it has been reported in widely scattered areas of the middle west the southwest California and the northwest Only the Atlantic seaboard has so far escaped an epidemic of this disease

Recent epidemiological evidence has revealed that the viruses of St Louis encephalitis and western equine encephalitis are quite similar though immunologically distinct Each is widely distributed in many animal hosts and transmitted by *insect vectors* Epidemics in which both agents appeared responsible have been reported and it is possible that simultaneous infection with the two viruses can occur in a single individual From the evidence of wide dissemination of these viruses it is feared that human infections will become increasingly prevalent and more widely recognized

Etiology—The *virus* of St Louis encephalitis was discovered by injecting mice and monkeys intracerebrally with bacteria free brain suspensions obtained from fatal human cases Monkeys develop an encephalitis but recover while mice uniformly die By neutralization tests it has been demonstrated that the serums of patients who recover from the disease protect mice against an otherwise fatal infection whereas the serums of patients recovered from lethargic encephalitis Japanese B encephalitis Australian X disease and equine encephalitis fail to protect mice infected with the St Louis virus Thus there is proof that the new virus is antigenically distinct from all other known encephalitis viruses and that the disease constitutes a separate etiological entity St Louis virus can be grown in tissue culture and on the chorio-allantoic membranes of fertile hens eggs

Epidemiology—*St Louis encephalitis differs strikingly from lethargic encephalitis in its* seasonal prevalence Whereas the latter occurred chiefly in the colder months of the year the first outbreak and all subsequent epidemics of the St Louis type have occurred in the *summer* and *early fall*

The *age distribution* of the 1933 epidemic was quite remarkable in that the majority of the patients were older people The attack rate was ten times as high in persons over 60 as in children under 10 *Sex and economic status appeared to play no role More cases in propor*tion to population occurred in rural and suburban areas than in the city proper Multiple cases in families were rare and there was no evidence of direct person-to-person transmission

In subsequent *epidemics the age distribution of patients has continued to show a pre*ponderance of adults but it is not so marked as in the original epidemic It is possible that differences in exposure to infection rather than susceptibility account for these variations

Rapid strides *have been taken in advancing our knowledge* of the epidemiology *of this* disease but until such information is reasonably complete control measures cannot be planned intelligently It has been found that a large number of domestic fowl *and* livestock as well as some wild *species have neutralizing* and complement fixing antibodies in their *serums for this* virus which suggests previous inapparent infection Infection of both man and animal points to the likelihood of a common *insect vector* Although the search for such a vector was fruitless during the 1933 epidemic the possibility of *mosquito transmission* was considered purely on the basis of epidemiological data This supposition has subsequently been confirmed by the finding that the mosquito (*Culex tarsalis*) may harbor the virus and is presumably the vector both to *animals and to man Whether other insect vectors also exist remains to be determined*

Pathology—The pathology of St Louis encephalitis is that of a *non-suppurative inflammation of the brain* characterized by marked vascular congestion perivascular cuffing by small round cells and focal accumulations of cells unrelated to blood vessels Degenerative changes in nerve cells with neuronophagia are also seen While the damage is most marked in the brain stem the cortex is also involved but cranial nerve nuclei are generally spared Although the inflammation of the brain is more widespread than in lethargic encephalitis the pathology is essentially similar

Clinical Manifestations

During the 1933 epidemic in St Louis the *incubation period* was estimated at six to fourteen days and in the 1940 Yakima Valley outbreak

Nonsuppurative Encephalomyelomeningitides

The differential diagnosis of the nonsuppurative encephalomyelomeningitides is neither a satisfactory nor a rewarding discipline since only rabies and syphilitic meningitis respond to preventive or curative therapy Nevertheless it is the duty of the practitioner to attempt classification for reasons of public health and for prognostic implications Certain of the infections notably anterior poliomyelitis St Louis encephalitis and lethargic encephalitis occur in epidemic form and require notification of the health authorities so that efforts may be inaugurated for limiting the propagation of the disease Some of the infections are reasonably benign (lymphocytic choriomeningitis) whereas others as illustrated by tuberculous meningiti are universally fatal

Epidemiologic data are of value in the presence of an epidemic but satisfactory establishment of the diagnosis in early cases and in sporadic disturbances rests upon complicated laboratory procedures that are the province of special investigators particularly in the laboratories of the United States Public Health Service

The table which follows lists only the infections which are encountered in the United States Additionally Japanese B encephalitis and Russian seasonal encephalitis respectively are recognized in these countries There seems reason to believe that the Japanese variety is closely associated with the St Louis encephalitis of the United States Russian seasonal encephalitis thus far has not been clearly identified with any of the American varieties

	Season	Age and Sex	Cerebrospinal Fluid			Serum		Pathognomonic Feature
			Appearance	Cell Count	Differential	Virus Neutralizing Bodies	Complement Fixation	
Rabies	Any	Any	Clear	0 to 100	Polymorphonuclears	+	+	Dog bite
Epidemic Encephalitis	Spring Winter	Adult Males	Clear	10 to 100	Mononuclears	—	—	Cranial nerve palsies Late sequels
ost Infectious ncephalitis	Any	Any	Clear	10 to 100	Mononuclears	—	—	History of measles varicella pertussis vaccinia mumps etc

have recovered from the disease contains *antibodies* which can be used for mouse protection tests or *complement fixation* The latter is simple rapid and specific and it is hoped that it will soon be available in laboratories to which the practitioner has access See *Differential Diagnosis of Nonsuppurative Encephalomyelomeningitides* (p 442)

Leukocyte counts of from 10 000 to 20 000 per cu mm with a preponderance of neutrophils are usual in St Louis encephalitis The *spinal fluid* is clear and commonly under increased pressure The protein content is increased but the concentration of sugar is normal The cell count varies from 50 to 500 cells per cu mm the majority being small *mononuclear cells*

Prognosis

The overall case fatality rate in all the reported epidemics of St Louis encephalitis is about 20 per cent The fatality rate varies markedly with age In the twenty to thirty year age group it is less than 10 per cent while in the age group over fifty it is more than 50 per cent

Most patients recover completely In general sequels are less common and less severe than in lethargic encephalitis A follow up report on the St. Louis epidemic indicates complete recovery in two thirds of the patients and mild symptoms of Parkinsonism in about 10 per cent Residuals most often noted are subjective complaints such as headache nervous irritability loss of memory and drowsiness

Treatment

No specific *serum* is available *Lumbar puncture* is thought to afford some relief from headache Because of the high case fatality rate anti infective therapy with oral sulfonamide and intramuscular and intrathecal penicillin is justified

Prevention

Successful *vaccination* of laboratory animals is reported but there is no safe vaccine which can be used for the prevention of the disease in man

ACUTE ANTERIOR POLIOMYELITIS (INFANTILE PARALYSIS)

Poliomyelitis is an acute infectious disease affecting the central nervous system and characterized by abrupt onset of fever gastro intestinal symptoms headache meningeal reaction and in a variable number of patients by the development of flaccid paralysis Intensive investigation has greatly expanded knowledge of the disease but specific measures for prevention and treatment are still lacking

Etiology—In 1909 poliomyelitis was reproduced in monkeys and the causative agent established as a *filtrable virus* Recently several strains of the virus have been transmitted to cotton rats and white mice and the successful cultivation of the virus in tissue culture preparations has also been accomplished.

The size and physical properties of the virus are well known It is remarkably resistant to physical and chemical agents which are antiseptic or germicidal to most bacteria It withstands cold temperatures for long periods In view of the fact that the poliomyelitis virus has been recovered in water and sewage it may be noted that concentrations of chlorine ordinarily employed in water purification fail to destroy it

Epidemiology—Poliomyelitis occurs sporadically and in epidemic form in the United States The first recognized epidemic in this country was in 1894 in Vermont. Since then an

spinal fluid is clear with moderately increased globulin concentration a normal sugar content and 10 to 100 cells mostly small mononuclears The fluid is bacteriologically sterile

When the disease was first recognized in Vienna *lethargy* and *diplopia* were the outstanding initial symptoms The patient became drowsy then stuporous and exhibited various degrees of *ophthalmoplegia* There was some *nuchal rigidity* but few signs of pyramidal tract involvement *Bulbar signs* such as hiccough and difficulty in respiration or swallowing were seen in severe and usually fatal cases At times the *paralysis agitans* syndrome developed rapidly without previous symptoms Later in the epidemic *mental symptoms* and *abnormal involuntary movements* such as chorea and myoclonic movements were prominent features of the disease *Insomnia* was more characteristic of cases late in the epidemic than drowsiness *Delirium mania* and *neuritic* or *radicular* pains were of common occurrence Mild and abortive cases were frequent perhaps more common than the frank and obvious cases

Course and Prognosis

The overall mortality is generally given at about 20 per cent but if the many mild and unrecognized cases are included it is probably much lower Some patients recover in a few weeks while in others the disease lasts for many months or becomes latent only to appear later in the form of sequels Chronic damage to the nervous system is very common and the late sequels include the *paralysis agitans syndrome ocular palsies oculogyric crises narcolepsy cataplexy mental retardation* and *personality changes* These sequels are as likely to occur after mild or abortive attacks as after the more severe forms of the acute disease A considerable number of patients seen for the first time with paralysis agitans or other evidence of chronic encephalitis give no history suggestive of an acute cerebral disease

Diagnosis

A *febrile disease* characterized by slight or moderate meningeal reaction and *widespread brain involvement* should suggest the diagnosis of encephalitis *Multiple sclerosis* and *syphilis* are the only common diseases which give evidence of such widespread and nonsystematic involvement of the nervous system The other known virus encephalitides (poliomyelitis St Louis encephalitis equine encephalomyelitis lymphocytic choriomeningitis) and the postinfectious encephalitides can be differentiated by history epidemiological considerations course of the disease and laboratory tests

Treatment

The treatment of acute encephalitis is entirely symptomatic There is no evidence that the anti infective agents have any efficacy in the treatment of lethargic encephalitis Nevertheless because of the dire consequences of this process the practitioner may be forgiven for indulging in what appears to be purposeless prophylactic chemotherapy It is our opinion that the patient should be given the opportunity of full oral doses of *sulfonamide* and injections of *penicillin* both intramuscularly and intra

e i ned ei tirely ell v hile the other l alf had mil l i pper respiratory and gastro-intestinal symptoms Only a few contacts ha l ym toms which are ordinarily con idered those of abortive nonparalytic pol omyelitis These observations empl asize that *the virus of pol o myel tis is w dely distributed* It re ults in mild and inapparent infections in most persons in *abortive poliomyel tis in others* and in frank paralytic disease in a small minor ty

Pathogen s s—Until recently it was generally bel eved that the common natural portal of entry of virus was the olfactory area of tl e nasal mucosa Tl ence it was presumed to pass along the olfactory nerves and bull s to tl e central nervous system This belief was based upon ob rvations made on monkeys but it l as been found that they cannot be read ly applied to man Anatomical lesions of tl e olfactory bulbs are not commonly *found in fatal human cases* and virus l as not been recovered from this site altl ough present in other portions of the brain and cord

Tl ere is rapidly gro ing ev dence that *tl e po tals of ent y and exit ay be the pharyn geal and inte ti al mu osa* Monkeys can be inf cted by the ingestion of virus even after the olfactory p thway has been severed Virus may be excreted in the stools of pat ents for weeks and even mo ths after cl nical d ea e It therefore seems possible that it actually lo lges and multipl es in the intestinal all

There is no evide ice tl at tl e virus becomes g ne a ly li tributed throi gl out the tis ues of the body *Within tl e nervous syst m it is prese t in eurons ather than in the supportin* tis ues and it preads along axonal pathways Whate er tl e portal of entry virus reaches tl e c ntral nervous sy tem by way of tl e somatic or autonomic nerv s

Recent tons lle tomy appears to favor tl e de elopment f b lbar poliomyel tis This ould si gge t that the trauma of the operati n favors the ntrance of v rus through the pl ary eal muco a and its pa age to tl e medulla

Pathology—In fatal cas s the distribution of virus and the pathol gical involvement of the central nervous sy tem are much more wide p ead tl an would be i d cated by tl e amount of p ralysis Edema and perivascular infiltrat on with mall rou d c lls oc w lely through out the brain and sp nal ord Actual d struction of nerve cells i lim ted mo tly to tl e mot r or anterior l o n cells of the sp al co d h efly in the cerv cal or lumba reg ons and to th m tor c lls of the medulla As the acute illness sub ides those cells which l a e been only partly injured recover their function wl ile those which have been dest ov d disintegrate and a e remo ed by pl agocyt s Tl e nerve trunks which ari e from these dead cells und go de ene ation v tl re ult n*w paralys s of the muscles they innervate*

CLINICAL MANIFESTATIONS

The *incubation period* of poliomyeliti is thought to vary between four and eighteen days and the majority of infections are either *inap parent* or *abortive*

PRODROMES INAPPARENT AND ABORTIVE REACTIONS

The symptoms of the initial illness are mild and so lacking in specific characteristics that a clinical diagnosis cannot be made although it may be suspected in the presence of an epidemic Mild fever nausea vomiting anorexia and symptoms of upper respiratory infection lasting two or three *days constitute* the initial manifestations If nothing further develops the disease represents an *abortive attack of poliomyelitis* but in the ab sence of elaborate laboratory studies the diagnosis cannot be made with certainty

PREPARALYTIC STAGE

In a minority of cases after a latent period of several days during which the initial symptoms may be forgotten a *recrudescence* of symp toms occurs In this preparalytic stage fever and prostration are more marked signs of involvement of the nervous system appear and paral ysis may or may not subsequently develop

In the pre paralytic stage the patient develops fever and prostration

MEASLES ENCEPHALITIS

Complications of the central nervous system follow measles more frequently than any other acute infectious exanthemas Nevertheless considering the universal prevalence of the disease encephalitis is an extremely rare complication There seems to be no relation between the severity of the attack of measles and the incidence of encephalitis

The onset of the nervous disease usually occurs suddenly while the measles rash is still present or soon after the beginning of convalescence Fever and headache are almost constantly present and mental symptoms include drowsiness stupor coma delirium or apathy Signs of meningeal irritation are present in half of the patients and convulsions in a third Cranial nerve palsies and spastic or flaccid paralyses of the muscles of the extremities are occasionally present

Spinal fluid pressure is usually increased and the cell count is generally less than 100 cu mm with mononuclear cells predominating The protein and sugar contents are normal or moderately increased There is no obvious relationship between the spinal fluid changes and the severity or prognosis of the clinical state This principle applies equally well to the other postinfectious encephalitides

The course of the disease is quite variable lasting from one week to many months From 10 to 20 per cent of patients die during the acute stage of encephalitis While the majority of the others make complete recoveries a considerable proportion show a variety of residua of greater or lesser severity including personality changes grand and petit mal attacks mental deterioration and various palsies

ENCEPHALITIS FOLLOWING GERMAN MEASLES

Central nervous system complications of German measles seem to be extremely rare They follow shortly after the appearance of the exanthem The symptomatology and course are similar to those following measles

VARICELLA ENCEPHALITIS

Chickenpox may be complicated by encephalitis in a very small number of patients It occurred in five out of more than 2000 cases seen at the Willard Parker Hospital

The onset is usually between two and eight days after the appearance of the rash The symptomatology resembles the encephalitis which follows measles but the patients on the whole are not so severely ill and the prognosis as regards complete recovery is better The spinal fluid findings are similar to those of measles encephalitis

POSTVACCINAL ENCEPHALITIS

See p 440

NEUROLOGICAL COMPLICATIONS OF ANTIRABIC TREATMENT

The most comprehensive observations on the neurological complications of antirabic treatment have been made in France where about 500 cases were reported among more than a million persons vaccinated Nearly all were adults The onset occurred during the treatment in two thirds

of infections the presence of 50 or 100 afflicted children makes headlines in local newspapers which would pay no heed to an equal number of examples of pneumonia whooping cough or syphilis

It is an unfortunate truth that the practitioner must be somewhat in fluenced in his therapeutic routine by this mass hysteria Parents who would normally sit out an attack of scarlet or rheumatic fevers demand active therapy no matter how remote the chance for relief

Immunotherapy—*Normal and convalescent human serum* has been utilized in epidemics of poliomyelitis Because of the variation in the course of the disease (p 4 9) it is quite impossible to make a definite evaluation of the success of these measures The majority of objective practitioners have no great enthusiasm for these modalities whether given intravenously intramuscularly or intrathecally Large doses of gamma globulin given intramuscularly in the preparalytic stage produced no detectable benefit in a carefully studied series of 111 patients

The Antibiotics—The antibiotics do not appear to have any specific value in the treatment of poliomyelitis Neither sulfonamide (p 88) nor penicillin (p 106) has produced any satisfactory result and there is little hope that more can be accomplished by streptomycin (p 104)

The Kenny Treatment—The Kenny method of treatment is based on the concept that the symptoms of infantile paralysis are due to *muscle spasm incoordination* and *mental alienation* of non affected muscles Temporary contractures are part of the muscle spasm which, if unattended develop into fixed deformities Uncontrolled voluntary motion when attempted in the presence of spasm leads to the development of abnormal patterns of motion which present themselves as the symptoms of incoordination Mental alienation is the inability to produce a voluntary movement in a muscle in spite of the fact that the nerve paths to that muscle are intact

The execution of this method of treatment is not for the amateur It requires well trained physical therapy technicians or graduate nurses The treatment must be supervised and checked by the specialist physician in charge

Treatment is begun as soon as the diagnosis is made preferably in the acute stage during the period of quarantine Hot fomentations are applied to the parts which are in spasm woolen cloths are cut to fit the parts accurately these are placed around a light waterproof covering Both of these coverings are spread out accurately under the area to be treated The hot foments of flannel are boiled and wrung from the boiling water twice through a very tight wringer so that as much water as possible is removed These are placed directly and as quickly as possible over the affected part Joints are not covered The hot packs are removed every fifteen minutes to every hours depending on the severity of symptoms This is continued without interruption throughout twelve hours of each day The alternate heating and cooling of the parts seems to be a factor in relaxing the spasm

Passive motion through the range that can be obtained without pain is carried out once a day Neither muscle testing nor re-pir tors are permissible

Muscle reeducation is included in the Kenny method to restore mental awareness or to connect the part with the central nervous system The first aim of treatment is the production of a normal rhythmic motion Increase in muscle strength follows

As soon as joints can be moved passively through a small range of motion without pain or incoordination muscle reeducation is begun while the patient is still in bed The first step is the education of the patient to a mental awareness of the muscles and their insertions Active motions are prohibited until passive motion can be carried out by the technician with complete relaxation of the patient Incoordination or the use of other muscles than the one called on is prevented Care is taken not to tire the patient

For details as to the care of specific muscles the reader is referred to the brochure on the Kenny method of treatment for infantile paralysis obtained from the National Foundation for Infantile Paralysis

It is now possible to evaluate more clearly the orthopedic management of poliomyelitis as enunciated by Sister Kenny It is the general opinion of those who have studied her method objectively and carefully that nothing is accomplished beyond what may be expected from the spontaneous course of the disease and routine physiotherapy by an expert

Pharmacotherapy—Relief of muscle spasm as attempted by physiotherapy in Kenny treatment, may be accomplished with the drugs neostigmine and curare

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Varicella Encephalitis

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Postvaccinal Encephalitis

See p 445

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LYMPHOCYTIC CHORIOMENINGITIS

Lymphocytic choriomeningitis is an acute infectious disease due to a filtrable virus The manifestations of infection with this agent are poorly recognized and little understood The form of the disease ordinarily recognized is an acute meningitis with bacteria free spinal fluid containing lymphocytes It runs a benign course with few complications but there is reason to believe that the virus of lymphocytic choriomeningitis may be responsible for various other clinical conditions some of which are by no means benign

Etiology—In 1935 the virus was isolated for the first time from the cerebrospinal fluid of two cases of acute aseptic meningitis When injected intracerebrally and intraperitoneally into mice guinea pigs or monkeys an encephalitic reaction is produced and the disease can be transmitted to other animals by injecting the infected brain tissue of the passage animals Animals injected with sublethal doses of virus develop neutralizing and complement fixing antibodies Several different strains of the choriomeningitis virus have been identified

Epidemiology—Lymphocytic choriomeningitis occurs sporadically in man No recognized epidemics have occurred All ages and both sexes are affected Most of the cases have occurred in winter and spring but a striking seasonal prevalence is not evident

The method of infection of man is unknown However Armstrong and others have noted that some patients gave a history of contact with *mice* Investigation of the homes of such patients revealed that some of the trapped mice were naturally infected with the virus or gave evidence of previous infection It is known that in mice the choriomeningitis virus is transmitted to the young by congenital infection It seems entirely likely therefore that rodents form a natural reservoir of infection Man may be accidentally infected by contact with them by ingestion of food contaminated with rodent excreta or by means of an insect vector These possibilities have not yet been thoroughly explored It is interesting that laboratory guinea pigs and white mice may carry the virus without evidence of disease

Pathology—Knowledge of the pathology of lymphocytic choriomeningitis is very meager as there have been few anatomical examinations in authentic cases of human infection In the few patients who died as a result of the meningo encephalitic form of the disease, the brain and spinal cord showed extensive inflammatory and degenerative changes Two patients who died of fulminating infection without neurological symptoms had pathological evidence of extensive pneumonitis In monkeys experimentally inoculated intracerebrally with virus there is a more or less pronounced lymphocytic infiltration of the choroid plexus and the pia mater Virus has been recovered from the blood stream lungs and other organs as well as the brain of fatal human cases

CLINICAL MANIFESTATIONS

Infection with the virus of lymphocytic choriomeningitis may be manifested by a number of clinical syndromes none of which is clinically unique It is only by the isolation of virus or the development of antibodies that the diagnosis can be made

Acute Benign Lymphocytic Meningitis—The clinical picture most generally regarded as typical of infection with the choriomeningitis virus is the syndrome of acute benign lymphocytic meningitis which usually begins fairly abruptly with *headache* but may be preceded by symptoms of *grippe* Often there is a latent period of a day or two between the respiratory illness and the onset of nervous symptoms Increasing headache vomiting and drowsiness or apathy with moderate fever are the usual complaints at onset Coma or convulsions are rare *Stiffness of the neck and back* are noted

Within a short time after onset clinical evidences of meningeal involvement are present in the form of *stiff neck* and a *positive Kernig sign*

possibilities A *vaccine* has been prepared and inactivated by ultraviolet ray which protects animals and does not confer the disease on those who are injected

Attempts to block the route of infection by treatment of the *olfactory mucous membrane* with alum picric acid and zinc sulfate have been abandoned It is by no means clear that infection occurs through these mucous surfaces

There seems to be conclusive evidence that bulbar poliomyelitis occurs more frequently in children who have been recently *tonsillectomized* On that account the operation should be postponed when there is a significant amount of poliomyelitis in the community

Passive immunization has been practiced widely during epidemics when public fear leads to a demand that *protective* inoculations be given Experimentally *convalescent serum* does protect monkeys subsequently inoculated with virus Whether normal adult or convalescent serum is effective in protecting children is not known despite extensive use It is probable by analogy with other types of passive immunization that the effects at best are of no more than a few weeks duration If given at all from 20 to 40 cc of adult or convalescent serum should be *injected intramuscularly*

After treatment—The after treatment of poliomyelitis requires the combined services of physiotherapist and orthopedic surgeon Splints and braces are used as supports against gravity and to protect weight bearing joints Re-education of muscles and operative orthopedic procedures may be required later in order to rehabilitate the afflicted child

especially in interepidemic periods may represent infection with the virus of choriomeningitis

Virus Pneumonia Type —Finally as a fourth type of infection with the choriomeningitis virus several fatal examples of what is generally considered virus pneumonia (p 2188) have been shown to be caused by this agent Whether the choriomeningitis virus is a frequent cause of atypical pneumonitis is not known At any rate it is one more virus to be added to the list of known agents which can produce the clinical picture

See *Differential Diagnosis of Commoner Febrile Intrathoracic Disorders* (p 404)

Diagnosis

The meningitic or encephalitic forms of the disease may be confused at times with a number of other conditions *Pyogenic meningitis* is ruled out by the character of the spinal fluid and the results of bacteriological culture *Tuberculous meningitis* is characterized by a reduction in the sugar content of the spinal fluid by the demonstration of tubercle bacilli in the sediment and by the invariably fatal outcome *Poliomyelitis* in the preparalytic stage is marked by more pain and muscle tenderness than is commonly found in choriomeningitis and the spinal fluid in this stage contains chiefly polymorphonuclear leukocytes

Other types of virus encephalitis may be distinguished with certainty only by laboratory procedures Both *St Louis* and *equine encephalitis* are epidemic summer diseases while choriomeningitis occurs sporadically and more often in the colder months of the year Even when all other likely infections are ruled out on clinical grounds it cannot then be assumed that the illness is actually choriomeningitis There are many cases of acute lymphocytic meningitis with a short course and favorable outcome in which the virus of choriomeningitis has not been isolated despite careful laboratory study There can be no question that this agent is only one cause of the syndrome of acute aseptic lymphocytic meningitis and that other agents remain to be discovered

The laboratory diagnosis of the disease can be made by the *inoculation of blood or spinal fluid* from the patient into mice and guinea pigs the diagnosis is established if the specific infection develops in these animals The blood and spinal fluid of patients usually contains virus only in the first few days of illness Recovery of the virus is not a procedure that can be carried out in routine diagnostic laboratories

See *Differential Diagnosis of Nonsuppurative Encephalomyelomeningitides* (p 442)

Following recovery the patient develops *complement fixing* and *virus neutralizing antibodies* The former appear during convalescence and persist for a few months while the latter develop about two months after the onset of the disease The neutralization test is a complicated procedure but the complement fixation test is simple and rapid and requires no animals

Treatment

There is no specific therapy for this disease Treatment is symptomatic *Lumbar puncture* is done for diagnostic purposes when there is evidence of meningeal or encephalitic involvement In patients with severe headache

there may be evidence of glandular follicular or pseudo membranous inflammation *Stomatitis* with vesicles and aphthous spots may be noted as well as enlargement of the *salivary glands* Often the affliction is accompanied by retention in the nasal accessory sinuses and there may also be *puffiness of the eyelids* and congestion of the *conjunctivae*

The physical examination reveals findings that are often disproportionate to the complaints At best there are evidences of an inflammatory process in the upper respiratory passages and some lymphadenopathy The presence of the latter led to the adoption of the term glandular fever The glands rarely if ever suppurate unless there is a superimposed complicating bacterial invasion

A *splenomegaly* is frequently encountered and leads to the suspicion that the fever is typhoidal in origin A *relative bradycardia* often strengthens this latter viewpoint The verisimilitude is furthered when as so often happens a *roseola* appears usually during the second week of the disease

Infectious mononucleosis is sometimes complicated by a variety of *rashes* There may be widespread *morbilliform* or *scarlatiniform eruptions* *Urticarial* and *vesicular* lesions are less frequently observed and on rare occasions there may be *petechiae* and *small ecchymoses* In our opinion many of the eruptive phenomena of infectious mononucleosis result from the administration of various drugs which the patient has tried in a desperate attempt to secure some degree of comfort These include salicylates antipyretics barbiturates and the various cathartics particularly phenolphthalein See *Dermatitis Medicamentosa* (p 3335)

Laboratory Data—Without laboratory assistance it is quite impossible to differentiate infectious mononucleosis from the majority of the common and many of the uncommon infectious diseases Reliance is placed upon the *blood count* and the *sheep cell agglutination* test of Paul Bunnell (p 468)

Hemogram—The diagnosis of infectious mononucleosis is best made by examination of the blood Unfortunately the characteristic findings may not develop until later in the course of the disease and they may not persist throughout the entire infectious process As a result the practitioner who does not have the good fortune to make the examination at the proper time will lack valuable assistance unless the data are repeatedly sought

Early in the course of the disease there is a *leukocytosis* that may reach 15 000 to 20 000 cells Later the absolute and relative numbers of granular leukocytes diminish while the lymphocyte count progressively increases

The certain recognition of the mononuclear cell of infectious mononucleosis *requires the expert opinion of the specialist hematologist* It resembles closely the large lymphocyte and the normal monocyte of the routine hemogram It is usually a large cell of considerably greater diameter than the erythrocyte and hence easily distinguished from the small lymphocyte which accounts for all but 3 to 6 per cent of the white cells other than the polymorphonuclears

The nucleus may be round indented horse shoe shape or bilobed The chromatin may be loose or dense the nuclear border is usually sharp and a clear perinuclear zone is demonstrable The cytoplasm is abundant and stains medium to dark blue It may be vacuolated *bubbly or smooth* and occasionally has granulations

The fact that the disease occurs naturally in horses led to a search for other hosts of which a great number and variety have been found including many types of wild and domestic fowl By the actual recovery of virus or by the demonstration of neutralizing antibodies in their serums wild ducks pheasants pigeons domestic fowl and prairie chickens have been found to be natural hosts of both eastern and western equine encephalomyelitis All evidence points to the fact that there exists a tremendous reservoir of susceptible and potentially infected animal hosts It is entirely probable that the horse is not the chief host but like man is accidentally or secondarily infected

The spotty geographical distribution of cases the occurrence of the disease in the summer months and the lack of evidence pointing to direct communicability from person to person suggest the possibility that *insect vectors* may transmit the infecting agent from one host to another In the Massachusetts epidemic it was thought that *salt-marsh mosquitoes* were the probable vectors It has now been demonstrated that the western strains of virus can be recovered from *Culex tarsalis mosquitoes* in epidemic areas They are regarded as one of the principal vectors but other insects are at least potentially capable of serving in this role The *assassin bug* and the tick *Dermacentor andersoni* are experimentally capable of transmitting the virus The occurrence of cases of the western type in dry areas free from mosquitoes, strongly suggests that ticks and chicken mites may indeed be vectors of importance

The close epidemiological relationship between equine encephalomyelitis and St Louis encephalitis has been mentioned elsewhere (p 451) Epidemics due to both viruses and concurrent infection with the two viruses in a single patient have been described In seasonal distribution animal hosts and insect vectors the two diseases are almost identical

Pathology—In fatal cases of the eastern type of equine encephalomyelitis the brain is markedly congested with flattening of the cerebral convolutions severe edema and evidence of cerebellar pressure cones On section the brain is softer than normal Histologically there is widespread involvement of nerve cells varying from early nuclear changes to complete disappearance Marked infiltration of polymorphonuclear leukocytes about destroyed nerve cells and around blood vessels is a prominent feature Demyelinization alone is not prominent except where destruction has occurred as a result of the inflammatory process The pia arachnoid shows diffuse meningitis most marked over the base The pathology is essentially that of an acute diffuse meningo encephalitis with widespread involvement of all parts of the brain

In the western type the signs of meningitis are minimal There is infiltration with polymorphonuclear leukocytes and small mononuclear cells particularly about blood vessels The latter are acutely congested and often thrombosed Hemorrhages are frequent In contrast to the eastern variety myelin alterations are common even in the absence of an inflammatory reaction

Clinical Manifestations

Eastern Type in Infants—In the 1938 outbreak in Massachusetts the only recorded human epidemic of the *eastern type* the onset particularly in infants was sudden with *high fever irritability* or *drowsiness* and *convulsions* The *anterior fontanelle* was tense and bulging and stiff neck was a prominent sign In some infants edema of the face and about the eyes was noted Muscular twitchings and tremors were commonly seen The course was generally acute and fatal cases proceeded to termination with mounting pyrexia is less than a week

Western Type in Infants—But for the most important difference that the case fatality rate has never been above 15 per cent, the symptoms of *western equine encephalitis* are quite similar Fever with temperatures as high as 107° F is common in both fatal and nonfatal cases Convulsions with muscle twitchings spasms cyanosis irritability drowsiness tremors and vomiting are the usual symptoms

Western Type in Adults—In the 1941 outbreak of the western variety a larger number of patients were observed than in any previous epidemic and most of them were adults Their symptoms and course were quite different from those described previously in young infants While there was an





Fig 71 —Mononu leosis N te normal monocyte in lower l ft l and corne of upper plat R main ng white cells are lymphocytes typ al of nfect ous mononu leosis Note l ght blue ta n of ytopl m as contrasted w th dark purple eccentric nucleus Note cartwheel arrangement of ch (matin in nucleus an l sm ll va u les n cyt plasm Note comp ati e s zes of rytl r cytes and lymphocytes

Blackf D amond an l Le t r Atl s of tl Bl od in Ch ld en The Comm wealth Fund

is more prominent and the development of flaccid segmental paralysis is almost always indicative of that disease The separation however can be made with accuracy by laboratory studies In fatal cases virus may be recovered from the brain and identified *Neutralizing antibodies* develop by the end of the first week of the disease so that in more protracted cases this can be useful in diagnosis More recently a *complement fixation test* has been devised which is specific for each type of equine encephalomyelitis and does not give cross reactions between the two types or between either of them and the viruses of St Louis encephalitis poliomyelitis or choriomeningitis Mild or abortive cases of equine encephalomyelitis also occur In California some of the contacts of frank cases had mild vague symptoms and 70 per cent subsequently developed virus neutralizing antibodies On the other hand of those contacts who remained entirely well only a few developed neutralizing antibodies See *Differential Diagnosis of Nonsuppurative Encephalomyelomeningitides* (p 442)

Treatment

There is no specific therapy and the chief therapeutic problem is the *maintenance of nutrition* which is depleted by stupor and anorexia Most patients can swallow fluids in adequate amounts when aroused but for those in deep stupor or coma nasal tube feeding or intravenous fluid is required *Lumbar puncture* may be of value in relieving headache and other symptoms of increased intracranial pressure For delirium and restlessness bromides and chloral hydrate by rectum are beneficial Sulfonamide and penicillin (p 106) may be given as prophylactics against the development of secondary pulmonary infection A hyperimmune rabbit serum has been used successfully in the treatment of the experimental disease

Prevention

The virus of equine encephalomyelitis is too widely disseminated among many animal hosts to be easily eradicated *Mosquito control* measures may offer some hope of successful prevention

Since the disease in horses is of great economic importance a *vaccine* was prepared from a formalin suspension of virus grown on the membranes of developing chick embryos More than half a million horses were immunized with an apparent reduction in morbidity and mortality rates Such immunity is probably of temporary nature and must be repeated at yearly intervals A similar vaccine has been administered to human beings with only minor reactions resulting but there is no clinical evidence of its effectiveness although circulating antibodies develop It may be advisable to immunize persons living in epidemic or endemic areas and those exposed to special hazards of infection such as laboratory workers

ST LOUIS ENCEPHALITIS

In the summer of 1933 there occurred in the city and surrounding county of St Louis Missouri an epidemic of over 1000 cases of a hitherto unrecognized form of encephalitis On clinical and epidemiological grounds the disease was distinguished from encephalitis lethargica Since 1933 outbreaks of greater or less magnitude have been recognized but with ever widening geographical distribution Another epidemic of the disease

Nonspecific Treatment —*Symptomatic treatment* consists in the use of the remedies that are commonly employed in the treatment of the common cold (p 394)

ACUTE INFECTIOUS LYMPHOCYTOSIS

Acute infectious lymphocytosis is a specific syndrome with both sys temic and hematological manifestations The patient presents evidences of a febrile illness the lymph nodes and spleen are not enlarged but the total white count is elevated and the differential smear shows 70 to 80 per cent of small lymphocytes The heterophile antibody reaction is negative and there is neither anemia nor thrombocytopenia The bone marrow shows the same increase in the small lymphocytes as does the peripheral blood

The constitutional signs persist for several days The abnormal blood figures remain for 3 to 5 weeks The prognosis is invariably favorable and treatment is purely symptomatic

INFECTIOUS LEUKOPENIA

Infectious leukopenia is probably a variant of infectious mononucleosis The characteristic finding is the low white cell count which may be but 2000–3000 per cu mm

The disease is benign and must not be confused with the aleukemic phase of a leukemia or the agranulocytosis due to poisoning with amido pyrine The latter is excluded by the history the elucidation of the former may require bone marrow studies by an expert hematologist

There is no specific form of treatment but drug therapy should be most cautious

LYMPHOPATHIA VENEREUM

Lymphopathia venereum has been variously known as *climatic bubo tropical bubo esthiomene poradenitis Nicolas Favre disease* and *lympho granuloma venereum* It should not be confused with *granuloma inguinale* (p 475) which is an entirely different entity

Lymphopathia venereum is a specific venereal infection caused by a filtrable virus It is characterized by a transitory primary lesion followed by subacute inguinal lymphadenitis a tendency toward suppuration and fistula formation In the chronic stages there occur ulceration or ele phantiasis of the genitalia and rectal stricture It has only been since the application of the Frei test that the various clinical stages have been recognized as manifestations of a single disease

Etiology —The *virus* is present in the pus of inguinal buboes and has been recovered from the tissues excised from cases of rectal stricture Injected intracerebrally in monkeys and in mice it produces a fatal encephalitis Its particle size has been shown to be similar to that of vaccinia virus It can be propagated in tissue culture and in the yolk sac of developing chick embryos A potent antigen for Frei tests has recently been obtained by the latter method

By means of *complement fixation tests* it has recently been shown that the lympho-granuloma inguinale virus is antigenically closely similar to the virus of psittacosis What the ultimate significance of this finding may be is as yet not clear

Epidemiology —Lymphopathia venereum is a *widely prevalent disease* Next to syphilis and gonorrhea it is probably one of the commonest venereal infections It was formerly considered to exist only in the tropics and was seen chiefly in Europe and America among sailors returning from those regions Since the introduction of the Frei test however it has

it was about one week In the first epidemic there was often a *prodromal period* of headache malaise lassitude and sore throat before the onset of encephalitic symptoms In other patients the onset was sudden with *high fever mental confusion* and *stiff neck Headache* was very severe and signs of *meningeal irritation* were regularly present *Pyramidal tract involvement* was indicated by hyperactive deep and absent abdominal reflexes Coarse *tremors* of the extremities were noted and *cranial nerve involvement* was common In contrast to lethargic encephalitis ocular symptoms were rarely recorded Apprehension mental confusion delirium tremors of the lips and tongue and stupor were frequent, but deep coma was unusual

In many patients there appeared to be two phases in the disease There was first a *systemic reaction* with fever malaise chills and headache Often the temperature declined only to rise abruptly with the later development of signs of *meningeal and brain involvement* In other patients the latter symptoms predominated from the onset Fever was highest during the first few days of the illness and was generally normal within a week or ten days after onset Complete recovery was the rule within a week or two but fatal cases declined rapidly after onset with deepening stupor and mounting fever Many mild cases were encountered the patients complaining only of a little fever malaise and moderate headache On careful examination they were found to have some stiffness of the neck Were it not for the fact that they occurred during the course of an epidemic spinal puncture would probably not have been done

The clinical symptoms and course of the disease in a more recent epidemic (Yakima Valley 1940) were similar to those described in St. Louis In most patients the *onset* was sudden and with no more than a few hours of prodromal malaise and mild headache Influenza like symptoms such as myalgia and arthralgia were frequent and severe in the first few days of the illness *Abdominal pain* probably due to muscle tenderness was noted in the majority of cases *Photophobia* was a common symptom but jaundice was rare The complete picture of the disease with stiff neck headache drowsiness and gross tremors was fully developed within three days of onset The maximum temperature ranged from 103° to 106° F and was reached in from two to six days In the majority of patients essential recovery or a fatal outcome took place within a week of onset

Studies made in areas where the disease is or has been epidemic show neutralizing antibodies in the blood of a considerable proportion of persons who have had no contact with cases and who have had no recognized illness resembling encephalitis It seems likely therefore that inapparent infection or mild abortive attacks of this disease must occur with some frequency Whether the presence of antibodies is indicative of complete immunity to reinfection is not known

Diagnosis

There are no certain clinical criteria by which the St Louis type of encephalitis can be distinguished from *equine encephalitis lethargic encephalitis poliomyelitis of the nonparalytic type* or *lymphocytic choriomeningitis* The etiological diagnosis rests on laboratory data which appear to be reliable and clearcut The serum of patients who are convalescent or

the venereal diseases may coexist and he will not rest until he has definitively established the presence of any one and definitively excluded the presence of the others See *Differential Diagnosis of Dermatoses of Genitals and Perineum* (p 290)

A *complement fixation test* using an antigen made from the yolk sac of the chick embryo has also given preliminary satisfactory results and may supplement the information obtained from the Frei test

Frei Test—The introduction of the Frei test provided a simple and reliable diagnostic tool *The Frei test is negative in the very early stages of the disease but is positive in 95 per cent of cases with inguinal buboes and rectal strictures* As originally devised Frei aspirated pus from buboes and injected intradermally 0 1 cc of this material A positive reaction consisted in the development of a papule 0.5 cm in diameter surrounded by erythema and surmounted by a vesicle This appeared within 48 hours and persisted for several days Difficulties in obtaining sufficient amounts of pus from human cases led to the preparation of an *antigen* from *infected mouse brain* but this frequently gave false positive reactions Recently an antigen has been prepared from *yolk sacs* of developing chick embryos infected with lymphopathia virus By differential centrifugalization the virus is obtained in a highly pure state It is then inactivated with formalin and 0 1 cc is injected intradermally The reaction is read within 48 to 72 hours and a positive test consists in the development of a papule 6 mm or larger in diameter See Fig 72

The Frei test does not necessarily indicate the presence of active infection It apparently remains positive indefinitely and in the absence of all clinical manifestations

See *Differential Diagnosis of Dermatoses of Genitals and Perineum* (p 290)

TREATMENT

The introduction of the *sulfonamide* drugs has revolutionized the treatment of this disease Under sulfonamide therapy the involved nodes recede without suppurating and if discharging sinuses are already present they tend to heal Benefit has even been reported in cases of rectal stricture but when this is advanced mechanical dilatation or surgical intervention may be required *Sulfadiazine* is given in doses of 2 to 4 gm (30 to 60 gr) per day for ten to fourteen days followed by a rest period of a week A second course may then be given if indicated

The success of sulfonamide therapy has quite overshadowed older forms of treatment such as injections of *Frei antigen* as a vaccine and the use of *gold* and *antimony*

When permanent damage has been caused by the virus of lymphopathia venereum it may be necessary to institute mechanical therapy Digital or bougie *dilatation* may be required for a fibrous stricture of the rectum if obstruction occurs it may be necessary to perform a *palliative colostomy*

PSITTACOSIS

The occurrence of pulmonary infection in man as a result of contact with sick parrots has been recognized since 1880 but it was not until 1930 that it was established that the disease is caused by a non bacterial filtrable agent In the spleen liver and other organs of infected parrots and

increasing number of cases have been reported The largest epidemic in the United States occurred in 1916 with 30 000 patients affected In different years poliomyelitis appears to be prevalent first in one section of the country and then in another

Poliomyelitis is primarily a *disease of childhood* rather than of infancy It occurs with maximum frequency in children five to ten years of age and is slightly more common in males than in females In recent decade however an increasing tendency has been noted for cases to develop in adults and some epidemics such as that in Los Angeles affected adults almost exclusively Since poliomyelitis is not primarily a disease of infants and paralysis is not its commonest manifestation the name infantile paralysis is distinctly inappropriate

Poliomyelitis is a *summer disease* In northern United States the maximum number of cases occur in September and in the southern states they appear in June and July The relationship to temperature has suggested the possibility of *insect vectors* The disease is primarily one of temperate latitudes and is rare in tropical regions although its distribution is worldwide

Even during epidemic periods the attack rate is low and cases are sporadically *There is little evidence of direct infection from patients to contacts* When multiple cases occur in the same household they develop simultaneously or in rapid succession suggesting a common source of infection rather than communicability from case to contacts

The fact that most patients do not develop paralysis has led some investigators to believe that constitutional or hereditary factors favor the development of paralysis in certain persons and not in others Some maintain that patients who develop paralytic poliomyelitis have a characteristic physical and endocrine constitution

Immunity —Most of our knowledge of immunity to poliomyelitis has been derived from studies of *virus neutralizing antibodies* in the serum of recovered patients and normal persons The test is done by mixing suspensions of virus with human serum and then inoculating the test animal If the animal fails to develop the disease the human serum must have contained neutralizing antibodies There is some doubt as to the specificity of these tests since convalescent poliomyelitis patients may have less neutralizing antibodies in their blood serum than normal individuals

Neutralizing antibodies are widely present in adults Thus Aycock found that 0 per cent of a small group of adults living in large cities had immune bodies in their serum whereas only 20 per cent of adults from rural areas had neutralizing antibodies This would indicate that contact with the virus and a resulting immunity is more common in cities than in rural areas This agrees with the epidemiological observation that *poliomyelitis is primarily an urban or suburban disease*

Aycock also found that infants under one year of age had neutralizing antibodies which are probably passively transferred via the placenta from the mother A much smaller percentage of children than adults have neutralizing antibodies These studies are generally interpreted to mean that infection with poliomyelitis virus is widespread Since actual paralytic cases are few the implication is that the *majority of individuals develop subclinical and inapparent attacks of abortive poliomyelitis which result in active immunity* It is considered doubtful that natural immunity develops in man in the absence of contact with the virus

Transmission —More uncertainty exists as to the method of transmission of poliomyelitis than in most of the common infectious diseases of man Since the virus has been recovered in the nasopharynx *droplet transmission* has been regarded as probable On the other hand the summer prevalence of the disease is quite unlike that of other diseases in which transmission is through the respiratory secretions *Insect vectors* have long been suspected on the basis of the sporadic nature of the cases as well as the seasonal prevalence but until very recently there has been no proof of this A few epidemics have occurred which appeared to be *milk borne* but the evidence was never conclusive

A great advance has been made with the disclosure that the virus is present in large amounts in the stools of patients and contacts and can easily be recovered from such sources Virus has been recovered from *sewage* in the vicinity of cases of the disease *Common house flies* caught in the environs of the homes of patients have been found infected with virus Whether they are actual vectors of the disease or are merely mechanically contaminated by excreta containing virus is not yet known At any rate these discoveries imply that infection may be via the gastro-intestinal tract and may put poliomyelitis in the class of typhoid and the enteric diseases so far as its method of transmission is concerned

In a recent small rural outbreak of poliomyelitis virus was recovered from the stools of four out of five patients and from 75 per cent of the intimate contacts Half of these contacts

[illegible]

[illegible]

[illegible]

[illegible] The mode of [illegible]

Clinical Manifestations.—[illegible] that resembles [illegible] "typhoid fever." There is an [illegible] In a recent [illegible]



Fig. 3.—Photomicrograph showing Donovan bodies in the purulent material obtained from a case of granuloma inguinale.

of the lips and buccal mucosa with intense chemosis of the conjunctiva and a generalized vesicular eruption were noted.

The viruses of psittacosis and ornithosis are antigenically related to another virulent infectious agent known as the virus of meningopneumonitis affecting mice. All of these in turn are related to the virus of trachoma and lymphopathia venereum.

GRANULOMA INGUINALE

Granuloma inguinale is an ulcerative granulomatous lesion of the genital organs and groin. It is infectious in origin and transmitted by sexual intercourse. The disease is common throughout the tropics and it is not infrequent among Negroes in the southern part of the United States.

Etiology.—Many years ago Donovan described short rodlike oval bodies found within the cytoplasm of large mononuclear cells in the lesions of granuloma inguinale. *Donovan bodies* are pathognomonic of granuloma inguinale and the diagnosis should not be made without demonstrating them in scrapings of the lesion. The significance of these bodies

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entiation of these two diseases is by no means simple There have been a number of instances in which both diseases prevailed epidemically in the same locality and at the same time The constitutional and encephalitic symptoms of poliomyelitis are rarely so prominent as in equine encephalitis and the development of flaccid paralysis in the latter condition is extremely uncommon

St Louis encephalitis occurs chiefly in adults uncommonly in children *Lymphocytic choriomeningitis* occurs sporadically never in epidemics has no seasonal prevalence and the diagnosis can be confirmed by the subsequent development of specific antibodies *Tuberculous meningitis* is characterized by a low sugar content in the spinal fluid and occasionally organisms can be detected in the sediment Its course is invariably fatal *Luetic meningitis* occurs in adults and is readily diagnosed by the positive Wassermann reaction in the blood and spinal fluid See *Differential Diagnosis of Encephalomyelomeningitides* (p 442) and *Differential Diagnosis of Commoner Febrile Skeletal Disorders* (p 192)

Poliomyelitis must be differentiated from other acute febrile diseases which produce paralysis One of the most frequent of these is *infectious polyneuronitis* (*Guillain Barre syndrome*) characterized by widespread involvement of peripheral nerves roots cord and brain There are always sensory disturbances as well as motor involvement and the spinal fluid contains few cells but a high content of protein

Prognosis

There is no definite parallelism between the severity of the febrile or meningeal reaction and the likelihood or the severity of developing paralysis As long as fever is present the process is active and further progress of paralysis is possible With the subsidence of the acute reaction the pathological lesion has passed its maximum After 48 to 72 hours any change may be expected to be in the nature of improvement

The prognosis is good as regards life during the acute disease The case fatality for poliomyelitis of all types varies from 2 to 15 per cent in different epidemics and in different sections of the country The mortality is lowest in the purely spinal type and is highest in the bulbar or bulbospinal forms of the disease

Emphasis has been focused on prognosis through the claims of Sister Kenny utilizing her highly publicized therapy If her statement is correct as to the mortality and morbidity of poliomyelitis it might well be concluded that her efforts were crowned with impressive success However a study of the spontaneous course of 70 patients over the period of several years reveals that only 10 per cent required braces or future surgery 72 per cent had barely detectable weakness 8 6 per cent had significant weakness but required no therapy and 8 6 per cent died In view of these figures it would seem that any therapeutic endeavor would have to exceed the 80 per cent of spontaneous recoveries before justifiable claims of specificity were raised

Treatment

There are few diseases which create so much panic as poliomyelitis An entire community may be alarmed by the presence of only a handful

See *Differential Diagnosis of Dermatoses of Genitals and Perineum* (p 290)

Treatment—*Tartar emetic* administered by parenteral injection is regarded as an effective form of treatment It may also be applied locally One course consisting of a total dose of about 1.3 gm (20 gr) cures the majority of patients Excellent results have also been reported using intramuscular injections of fuadin After an initial probatory dose of 1.5 cc the full dose of 3.5 to 5 cc is given at two or three day intervals until a total of 40 cc has been delivered in a course The course may be repeated if necessary (p 132)

Granuloma inguinale is further discussed in the sections on the Female Reproductive System (p 2592) and the Male Reproductive System (p 2457)

YELLOW FEVER (VIRUS AMARIL FIEVRE JAUNE GELBES FIEBER)

The development of the knowledge of yellow fever forms one of the most fascinating chapters in the history of medicine For many years it was firmly believed that yellow fever was transmitted by filth and fomites but Carlos Finlay of Havana alone maintained that the disease was transmitted by an *insect vector* His belief was finally confirmed by the brilliant and conclusive work of the United States Army Commission in Cuba in 1900 Reed Carrol Lazar Agramonte and their colleagues on this Commission proved that fomites are noninfectious that the disease is transmitted by *Aedes aegypti mosquitoes* and that the blood of the patient is infectious for mosquitoes during the first three days of the disease The mosquito becomes infectious for others about twelve days later and transmits the disease to susceptible victims by its bite This work pointed the way to the eradication of yellow fever By a vigorous attack on mosquito breeding the disease was virtually eliminated from Havana

Some years later it became evident that yellow fever also existed in the back country of South America away from the sea coast and in jungle regions where the *Aedes aegypti* does not exist This necessitated a search for another vector and for the probable animal reservoir of *jungle yellow fever* as it is called This search is still in progress However laboratory research has come to the aid of preventive medicine by the development of methods by which the virus can be grown in tissue culture for the production of artificial immunization

Etiology—Yellow fever is due to a *filtrable virus* Noguchi s claim that it is a spirochetal infection was due to an unfortunate mistake in clinical diagnosis since the spirochetes which he isolated were actually obtained from cases of Weil s disease The size of the virus has been measured by ultrafiltration methods and has been found to be one of the smaller of the pathogenic viruses The virus is readily killed by heat and drying When injected into *monkeys* it causes acute hepatic necrosis reproducing the pathology of the human disease In *mice* it produces an encephalitis and upon repeated passage in these animals a neurotropic strain can be developed Yellow fever virus is apparently antigenically unique in the sense that cross-protection or neutralization with other viruses cannot be demonstrated

Epidemiology—It was not so many years ago that epidemics of yellow fever swept the seaport cities of the United States At the present time yellow fever is confined to the Caribbean areas and the northern and east part of South America (chiefly the Amazon basin) and to the west coast of Africa *Aedes aegypti* on the other hand, is worldwide in distribution

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Treatment

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enough to produce exsanguination. Epistaxis and bleeding from the gums also occur. Albuminuria is a constant finding. It is far heavier than an ordinary febrile albuminuria and may amount to 3 or 4 gm. per liter of urine. In fatal cases complete anuria usually precedes death. Muscle twitchings and coma are prognostic signs of grave significance. In nonfatal cases improvement begins in three or four days and convalescence is thereafter rapid and uneventful. Complete restoration of liver and kidney function is the rule.

All variations in the severity of yellow fever may be encountered. Some infections, probably the majority, are entirely unrecognized and are proved only by the subsequent development of immunity. Other infections are abortive, manifesting the initial influenza-like symptoms of onset but without any evidence of hepatic or renal damage. In these instances only the presence of bradycardia suggests the diagnosis of yellow fever. In other cases the initial symptoms are severe but the late signs of renal and hepatic degeneration do not develop.

Diagnosis

In endemic areas the diagnosis of yellow fever is not difficult. The presence of virus-neutralizing antibodies in the blood cannot be used in diagnosis in the acute stages. Weil's disease (p. 360) is common in these regions also and produces a similar syndrome that is less acute. The isolation of the spirochete will prove the diagnosis. See *Differential Diagnosis of Jaundice* (p. 1051).

Prognosis

In severe yellow fever the mortality may be as high as 60 per cent, but it is undoubtedly very much less in endemic areas. Mild and even inapparent infections must be very common in such regions.

Prevention

Active immunization is at present the only preventive measure against jungle yellow fever, since the mosquito plays no part in the transmission of this type of the disease. At the present time the virus is propagated on chick embryos which are then ground up, filtered and frozen until ready for use. This vaccine contains an attenuated but living virus. Some fear was expressed that yellow fever might result from the injection of this material. However, more than two million persons have been immunized in Brazil without the development of this complication. Immunity lasts from one to four years after the injection of one dose of attenuated virus.

Recently it was reported in Brazil and in both the British and American armies that numerous instances of *jaundice* have occurred from two or four months after yellow fever immunization. The cause of this reaction has not been ascertained to date, but it appears to be established that *the jaundice is not due to yellow fever itself*. It is likely that some unknown infectious agent was introduced into the vaccine when supposedly normal serum was added to it in the course of preparation. The method of preparation subsequently has been changed and further instances of this complication have not been reported (p. 82).

Neostigmine—Intramuscular injections of 1 cc of 1 4000 neostigmine repeated at four hour intervals often produce significant relaxation of muscle spasm and give comfort so far as pain and hyperesthesia are concerned The results are not consistent nor constant but they warrant trial particularly in conjunction with Kenny treatment

Curare (Intocostrin)—Curare seems to promise to provide dramatic relief of pain and spasm in poliomyelitis through paralysis of motor end plates According to the method of Ransohoff who *introduced intocostrin therapy an initial dose of 0.9 units per kilo of body* weight is injected intramuscularly If no untoward effects are observed 1.5 units per kilo of body weight are given in ten hours The clinical effectiveness of the drug is attested by the relief of opisthotonos and of the spasms most markedly seen in hamstrings pronators and intercostals An hour after administration of the drug the dysphagic child may be able to swallow The pharmacologic antidote neostigmine is kept at hand In the presence of respiratory paralysis an intravenous injection of 2 cc of 1 2000 solution is given

Although curare may produce respiratory paralysis untoward effects have not yet been noted by the clinical investigators In some instances the dose has been safely repeated at the end of five or six hours when indicated Future studies should provide data on which to determine whether curare has mere palliative action or whether the drug additionally prevents late sequels

The Respirator—Dramatic and well publicized instances of the use of the *respirator* have created some confusion as to proper indications The use of the respirator is clearly indicated only when the respiratory difficulty is due to intercostal or diaphragmatic paralysis To be most effective and to do the most good it must be used early Careful frequent observation *of the patient is necessary to detect beginning signs of intercostal or diaphragmatic* weakness The appearance of cyanosis severe dyspnea and air hunger are late signs and indicate that the respirator should have been used long before Difficulty in breathing is often the result of pharyngeal paralysis as a result of bulbar involvement In such patients unless there is also intercostal or diaphragmatic paralysis the respirator cannot be expected to do any good

Spinal Drainage—The symptomatic relief of poliomyelitis has been attempted by spinal drainage Enthusiasts for this form of therapy claim excellent results but certainly the practice is not to be recommended unless the life of the child is in jeopardy Under these circumstances we should favor removal of the patient to the hospital where repeated taps could be performed until the pressure readings approximated normal

Summary of Active Treatment—1 Contact the local health authorities to report the infection and obtain assistance from the National Foundation for Infantile Paralysis

2 Place the child in a comfortable position This is usually accomplished with the child supine while the foot of the bed is raised Oral secretions in this position gravitate out through the mouth

3 Provide a catheter for suction-drainage of oropharyngeal secretions if necessary

4 Apply hot compresses These can be improvised in the home by wringing out a blanket with hot water from the tap ironing it with a very hot iron at the bedside until it is dry and making the applications at 15 minute intervals for one hour

5 Set up an intravenous drip and give 500 cc of 10 per cent dextrose followed by a continuous infusion of 5 per cent solution until fluids are freely taken by mouth

6 If inexperienced in the use of curare give 1 cc of neostigmine (1 4000) intramuscularly Prepare to repeat the injection at four hour intervals

7 If experienced in the use of curare and if a respirator is available give an intramuscular injection of 0.9 units per kilo of intocostrin Prepare to give a second injection of 1.5 units per kilo of body weight at the end of five six or ten hours as indicated Keep neostigmine (1 2000) on hand for intravenous injection on signs of respiratory paralysis

8 Consider the introduction of 20 to 50 cc of normal or convalescent human serum The injection may be made intramuscularly or by way of the intravenous drip

9 Consider spinal drainage if a diagnostic tap shows a marked increase of cerebrospinal fluid pressure

10 Obtain the services of a trained physiotherapist for Kenny treatment in conjunction with neostigmine or curare injection

11 If possible have a respirator in readiness whether or not there are evidences of respiratory embarrassment

12 Seek consultation with the orthopedist for assistance in the prevention and later treatment of deformities and disabilities

Prevention—Active immunization for infantile paralysis is within the realm of future

orchitis oophoritis mastitis and pancreatitis occur in a considerable proportion of patients especially in young adults

Etiology—Mumps belongs among the diseases caused by *filtrable viruses* It can be reproduced in monkeys by the injection into the parotid gland of saliva obtained from human patients The infectious agent has been passed through a number of animals and back again to humans reproducing the disease *Human patients and experimentally infected monkeys* develop complement fixing antibodies to an antigen made from infected monkey parotid glands The virus has not been transmitted to other animals nor has it been grown in tissue culture

Epidemiology—Mumps is of world wide occurrence and is most prevalent in winter and spring *In cities it is endemic with epidemic seasonal peaks* while in rural areas it is much less common and may be absent for several years at a time returning again in epidemic form The great majority of persons exhibit natural susceptibility to mumps and as a result 70 to 90 per cent of persons living in large cities are believed to contract the disease before reaching adulthood In cities 90 per cent of cases occur in children from five to fifteen years of age and infants appear susceptible A large proportion of rural dwellers may escape infection altogether in childhood and such persons remain susceptible in adult life This is borne out by the experience of the United States Army during World War I where it was found that the great majority of soldiers who developed mumps came from rural areas In civilian life mumps is not regarded as a serious condition In military establishments however especially when large numbers of susceptible individuals are rapidly brought together extensive epidemics of mumps may occur It is not widely appreciated that in World War I there were nearly a quarter of a million cases of mumps among American troops the disease ranking next to influenza and venereal infection as a cause of days lost through illness

Transmission—Epidemic parotitis is probably transmitted by *droplet infection* from case to contact Whether healthy carriers exist or not is unknown The saliva of patients is infectious for monkeys during the first two days of parotid swelling but is no longer infectious on the third day These observations suggest a relatively short period of communicability However communicability may be prolonged by the onset of swelling of the other parotid gland several days after the first one It is conventional on the basis of clinical observation to consider a patient infectious for others from a day before the onset of symptoms to the subsidence of glandular swelling which is generally about one week This rule should be followed in regard to isolation

Immunity—One attack confers permanent immunity Second infections undoubtedly occur but they are very unusual

Pathogenesis—While it is customary to think of mumps as a local disease of the parotid and other salivary glands and to regard other manifestations of the disease as complications there seem to be reasonable grounds for questioning this point of view *Orchitis* occurs in from 5 to 25 per cent of young adult male patients *meningitis* or *meningo encephalitis* and abnormalities of the spinal fluid without obvious clinical symptoms occur in about 10 per cent while *oophoritis mastitis* and *pancreatitis* are not rare Where examination has been possible the pathological process in these organs is similar to that in the parotids Moreover orchitis or meningitis may precede the development of parotitis or may even occur in the absence of the latter For these reasons it appears that *mumps should be regarded as a generalized disease affecting many organs simultaneously or in succession* We have no knowledge as to the route by which the virus *becomes generalized and reaches the brain and other organs* but presumably it is through the blood stream from the buccal mucosa

Pathology—The chief lesions in the parotid glands are edematous swelling disintegration of the acinar cells and infiltration of mononuclear cells and lymphocytes Healing takes place with regeneration of the secretory cells without scarring The histological picture in affected testes is similar Pain in both testes and parotid glands is explained by the sudden edema and swelling of the tissues enclosed in fascial layers or dense capsules If the pressure in the tissues is excessive and unrelieved the blood supply is compromised with death of tissue and eventual atrophy of the organ The anatomical nature of the testes makes this unfortunate outcome not uncommon

Clinical Manifestations

The *incubation period* of mumps varies from fourteen to twenty one days In severe cases prodromal symptoms precede local pain and swelling

CHAPTER 22

VIRUS INFECTIONS, MISCELLANEOUS

INFECTIOUS MONONUCLEOSIS (GLANDULAR FEVER)

INFECTIOUS mononucleosis is a self limited benign infectious disease that occurs sporadically and in epidemic form It is characterized by its protean manifestations most constant of which is a generalized lymphadenopathy The definitive diagnosis requires laboratory assistance in the identification of the characteristic mononuclear cells and the recognition of the heterophile *reaction of the blood serum*

Infectious mononucleosis seems to be closely related to the common upper respiratory infections such as the cold (p 391) and influenza (p 396) Like them it is probably of virus origin Unless it is specifically suspected and its manifestations sought it will be regarded as a disturbance that is rarely encountered However if blood examinations are made as part of the routine investigation of bizarre and particularly protracted respiratory infections infectious mononucleosis will be discovered with surprising frequency in private practice

Clinical Manifestations—Infectious mononucleosis is most common during early childhood and adolescence but may be seen in all age groups The onset and course of the disturbance show endless variation so that it is difficult to formulate a description of an average attack The disease may start suddenly or gradually Often the first symptom is *soreness of the throat* The *enlarged glands* may produce pain in the neck or soreness when the head is moved Usually there is low grade *fever* but at times the temperature rises as high as 104° F occasionally with *chills* The patient complains additionally of *malaise anorexia weakness profuse sweating* and *tenderness of the various enlarged lymph nodes* which may be most prominent in the neck but at times are inguinal In certain instances the manifestations are predominatingly *digestive* There may be *vomiting* with *abdominal pain* which may be due to enlargement of the liver splenomegaly or lymphadenopathy involving the abdominal chains of glands On rare occasions *jaundice* has been noted to add to the confusion Again the syndrome suggests meningeal irritation There is *stiffness of the neck* due to the enlarged cervical glands These also produce some *rigidity of the neck* which with *headache* and *fever* are sufficiently suggestive to require a *lumbar puncture* for diagnostic purposes

The disease may also appear to be a local disturbance of the upper respiratory passages or the eyes There is usually some *stuffiness of the nose* and there may be *epistaxis* The *pharynx* and *throat* are often sore and

Oophoritis—Oophoritis seems less common than orchitis possibly because it is more difficult to detect Lower abdominal cramps and tenderness to palpation should suggest this complication Atrophy of the ovaries does not result probably because the ovary can enlarge without being constricted by a capsule

Pancreatitis.—In rare instances of mumps nausea vomiting diarrhea and midabdominal or epigastric pain occur due to the development of acute pancreatitis *Jaundice* and *acute diabetes* have been described in the course of this complication but as a rule it subsides without sequels

Neurological Manifestations—Various types of involvement of the nervous system may occur Increased protein and cells in the spinal fluid without symptoms have been described How frequently this occurs is not known since routine lumbar punctures are not performed However in perhaps 10 per cent of adolescent or adult patients there are symptoms suggestive of meningeal and brain involvement including *stiff neck headache* and *drowsiness* The *spinal fluid* in these patients is often under increased pressure with elevated protein content and a *pleocytosis* of from one to several hundred small mononuclear cells The prognosis of mumps meningoencephalitis is good and permanent sequels are rare In addition to meningitis *peripheral neuritis* and *cranial nerve involvement* including *permanent deafness* have been described

DIAGNOSIS

Mumps must be differentiated from swelling of the parotid glands due to other causes and from other swellings of the neck and jaw *Postoperative parotitis* may or may not be suppurative It commonly occurs in persons with poor oral hygiene and is accompanied by leukocytosis

A history of intermittent swelling of the parotid without fever and in relation to eating suggests the possibility of *a stone in the parotid duct* producing intermittent obstruction

Other causes of parotid swelling such as *tumor* and *sarcoid* are readily differentiated from mumps by their gradual onset and chronic course

Cervical adenitis and swelling of the jaw due to dental disease can be distinguished from mumps by careful observation of the localization of the swelling When the parotid gland is involved the swelling is chiefly behind the angle of the jaw and below the ear so that the ear lobe is at the center of the tumor

The white blood cell count is usually elevated above normal in mumps with a relative and frequently an absolute lymphocytosis

PREVENTION

The intramuscular injection of *human convalescent serum* administered within one week of exposure will prevent an attack of mumps Sufficient observations have been recorded to indicate that this is a highly satisfactory and effective form of preventive therapy For children under the age of 15 8 to 10 cc are required but for adults the dose must be larger Protection lasts only about two weeks Intramuscular injections of 20 cc of gamma globulin derived from mumps convalescent serum significantly reduces the incidence of complicating orchitis

Preventive treatment is of value in epidemics among susceptible adults

Perhaps the simplest rule of thumb is the suspicion of mononucleosis when the cells of the differential count, other than polymorphonuclears and small lymphocytes, equal or exceed 10 per cent Stated in other terms infectious mononucleosis is suspected from the hemogram when 10 per cent or more of the cells are mononuclear and larger than erythrocytes

The opinion of an expert is important since the condition may conceivably be an acute leukemia with fatal prognosis as opposed to the mononucleosis of benign character

So far as the rest of the hemogram is concerned there are no characteristic changes in the erythrocytes thrombocytes or hemoglobin content In borderline instances the diagnosis may become apparent from the progressive blood changes in which the numbers of mononuclears steadily increase or in the recovery stages show evidence of disappearance

Heterophile Agglutination Test (Paul Bunnell)—In addition to the characteristic changes in the large lymphocytes patients with infectious mononucleosis exhibit a positive *heterophile agglutination reaction* The test is performed by mixing serial dilutions of the patient s serum with a suspension of sheep cells and recording the highest titer in which agglutination of the cells is observed The mechanism of this reaction is incompletely understood the serums of many normal persons give a positive reaction in low titer in the presence of serum sickness even higher titers can be demonstrated The test as ordinarily performed is therefore not specific for infectious mononucleosis However if there is any doubt as to the significance of the reaction the test can be repeated after preliminary absorption of the serum with a 20 per cent suspension of guinea pig kidney This procedure has the effect of absorbing out nonspecific substances If a positive reaction in a titer of 1 32 or greater is still obtained it is most likely that the patient has infectious mononucleosis

As ordinarily performed with unabsorbed serum a titer of less than 1 64 is not of diagnostic significance In the majority of cases of infectious mononucleosis the titer rises to 1 256 or higher by the end of the second week of illness and it may reach a titer of 1 1024 or more Were it possible to take frequent specimens of blood from all patients with infectious mononucleosis it is possible that the *Paul Bunnell test* would be positive in 100 per cent of cases As it is 60 to 70 per cent of patients have a positive test

Confusion may be engendered by the appearance of a *false positive Wassermann reaction* In the presence of mononucleosis and in the absence of a history of sexual exposure the practitioner is justified in withholding specific therapy meanwhile repeating the serologic tests at weekly intervals Unless the two diseases coincide or are associated his judgment will be rewarded by a progressive fall and then clearing of the Wassermann as the mononucleosis abates

Course and Prognosis—Infectious mononucleosis is distinctly a *nuisance disease* The febrile stage may last for two weeks to several months and the patient is often left in a debilitated condition for an additional span of time of equal duration As a result a feeling of well being is rarely re established for an entire season and the whole process may run along for as much as a year The lymphadenopathy splenomegaly mononucleosis and high titer of heterophile antibodies are also persistent Wassermann positivity begins to fade out when the febrile period terminates and later disappears completely

CHAPTER 23

MYCOSES GENERAL CONSIDERATIONS

UNTIL recent times medical mycology has been a neglected confused and unsatisfactory study The fungi being universally distributed had no more than nuisance value in the laboratory while they were regarded as pathogenic agencies in certain superficial dermatoses their participation in systemic disease was neither appreciated nor recognized

The greatest impetus to the study of medical mycology has resulted from the discovery of the amazing anti infective activity of penicillin a chemotherapeutic agent derived from the penicillium notatum

DEFINITIONS USEFUL IN MEDICAL MYCOLOGY

Ascospores —A group of spores usually 4 or 8 enclosed in a sac or ascum
Blastospore —A spore formed by budding
Conidia—Spores formed directly from the vegetative portion by abstriction budding or septate division
Endospore—A spore formed within an outer envelope
Hypha —The single threadlike portion
Mycelium—A network of matted mass of branching hyphae
Oidia —Arthrospores of cylindrical form
Oospores and Zygospores—The union of male and female spores produces an oospore the union of two similar spores forms a zygospore
Septa —The division of hypha formed by transverse partitions
Spores —Cells developed for the propagation of the species
Thallus —The actively growing vegetative organism as distinguished from the reproductive portions

CLASSIFICATION

Fungi belong to the vegetable kingdom they contain no chlorophyll True fungi or *eumycetes* are separated from the *schizomycetes* of bacteria and the *myxomycetes* or the lime molds

THE EUMYCETES

The eumycetes or true fungi are subdivided into three classes of medical significance the *phytomycetes* possess a nonseptate mycelium and zygospores the *ascomycetes* reproduce ascospores exhibit conidia and have septate mycelia the *hyphomycetes* have a septate mycelium and spores and conidia may be recognized

METHODS OF EXAMINATION

Fungi are recognized in clinical medicine by direct microscopy by the examination of stained smears by cultivation and animal inoculation and by the use of skin tests using antigens prepared from the protein derived from the uncontaminated organism

Direct Microscopy —Direct microscopy may be practiced after cleansing the affected part with 75 to 95 per cent alcohol and obtaining hair nails scales or bits of tissues scrapings from a moist surface washings from a sinus or a small biopsy specimen The material to be examined is placed

Relapses of the disease are occasionally seen and are usually of slight duration

Diagnosis—The diagnosis of infectious mononucleosis rests entirely on a high index of suspicion by the practitioner and his perseverance in studying the blood count and the heterophile titer Only the demonstration of positive laboratory findings warrants the adherence to the clinical diagnosis since the features of the disease may simulate syphilis leukemia tuberculosis typhoid fever meningitis catarrhal jaundice, acute appendicitis hepatitis pan sinusitis diphtheria influenza and the common cold

Treatment

The treatment of infectious mononucleosis is unsatisfactory There are available at the present time no specific therapeutic aids either in prevention or active treatment

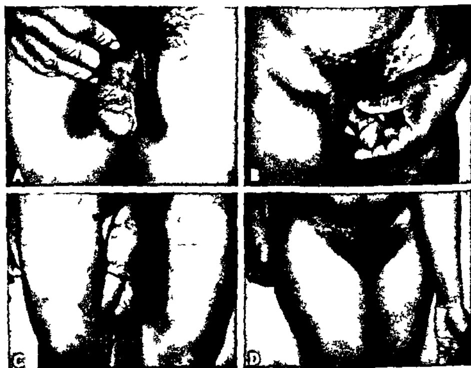


Fig 72—Lymphopathia venereum A Primary lesion of penis B Lesion of penis with bubo C Lesion of penis with elephantiasis D Bubo in female with positive Frei test of forearm

Immunotherapy—*Convalescent serum* has been employed with reputedly good results in a small number of patients The irregular course of the disease however makes it impossible to render an accurate evaluation

Chemotherapy—Sooner or later each patient with mononucleosis of more than moderate severity or of considerable persistence will be tried on sulfonamide therapy The results are certainly not encouraging

The *arsphenamines* have also been tried without significant effect *penicillin* is ineffectual

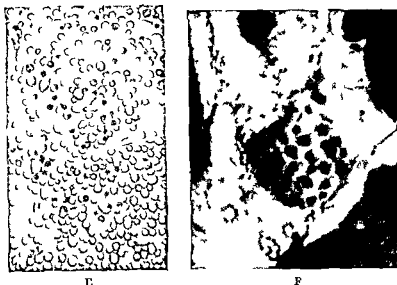


Fig 6—Mycoses E Monilia albicans Culture F Histoplasma in Kupffer cell of liver†

TABLE KEY TO IDENTIFICATION OF FUNGI BY DIRECT EXAMINATION‡

Spores and hyphae present

Spores of *conidial type* without buds found in and around hairs and cutaneous scales

1 Spores round diameter 2 to 4 microns irregularly arranged chiefly outside of hair *microsporon*

2 Spores spherical ovoid or cylindric 3 to 8 microns in diameter arranged in chains either within (endothrix) or outside (ectothrix) hairs *trichophyton*

3 Spores irregular in shape large both hyphae and spores relatively sparse so that the structure of the hair is always clearly visible between them air bubbles often present *achorion*

Spores are *yeastlike* often found detached from hyphae *monilia mycoderma endomyces*

Spores or yeastlike cells present *hyphae* absent

Budding forms

1 Small (3–5 microns) without hyaline capsules *torula* (cryptococcus)

2 Large (5–20 microns) with hyaline capsules budding infrequent *blastomyces* (zymonema)

Nonbudding forms

1 Round with refractile capsules 5–50 microns asci containing many spores may be found *Coccidioides immitis*

2 Cigar shaped nonseptate bodies 3 to 10 microns long 1 to 3 microns wide very difficult to demonstrate sometimes found in macrophages *sporotrichum*

Hyphae or mycelial masses found without spores

Hyphae made up of oblong double contoured cells invade epidermis but not hairs *epidermophyton*

Mycelium has few septations oval cells (not true spores) sometimes present *aspergillus*

Entire fungous mass characteristic sulfur granules yellow or dark brown in color When crushed there is a central area of fine interlacing threads and a peripheral zone of clubs which are the swollen ends of some of these threads *actinomyces*

Lewis and Hopper An Introd to Medical Mycology The Year Book Publishers Inc
† Courtesy of Dr Norman F Conant Duke University
‡ After Stovall and Alemon in Diag Procedures and Reagents APHA 1941

been recognized that the disease is quite prevalent in this country especially among Negroes

Pathology—The virus tends to spread from the primary site of inoculation by means of the lymphatics to regional lymph nodes This fact largely explains the differences in clinical manifestations between males and females In the former lymphatic drainage from the penis is toward and into the inguinal lymph nodes and thence to the deep inguinal glands The disease in males is therefore characterized by an inguinal lymphadenitis On the other hand, in the female the posterior fourchette the vagina and the cervix are supplied with lymphatics which drain into the perirectal and retroperitoneal glands Hence infection in this sex is more likely to produce rectal stricture and chronic fistulous lesions of the perineum (*esthiomene*)

Pathological changes in the involved lymph nodes are those of a subacute granuloma with multiple abscess formation Histologically there are minute inflammatory foci and later small abscesses and necrosis of the glandular structures

Clinical Manifestations—The *incubation period* varies from a few days to several weeks The *primary lesion* occurs on the penis the labia minora posterior fourchette or cervix It is an evanescent lesion which is not recognized in the majority of cases Occasional cases of extragenital infection have been reported with the primary lesion located on the face neck tongue tonsil or finger and the adenitis confined to the regional lymph nodes draining those sites The primary lesion may take the form of a vesicle ulcer papule or nodule and it may cause a urethritis (p 2336)

The *invasion of the regional lymph nodes* marks the second stage of the disease Pain and stiffness in the groin are followed by swelling and tenderness in the inguinal nodes Involvement may be unilateral or bilateral Constitutional symptoms commonly present at this stage include *moderate fever* and *leukocytosis chills sweats prostration anorexia nausea* and *vomiting* Occasionally *meningeal symptoms* and *splenomegaly* are encountered suggesting that the virus may become generalized throughout the tissues of the body As the adenitis progresses areas of softening develop and eventually the nodes tend to become matted together and adherent to the overlying skin Multiple *sinus tracts* form and the discharge of pus may continue for weeks or months Eventually healing takes place with *extensive scarring* (Fig 72 p 470)

The later stages of the disease are characterized by *chronic ulceration rectovaginal fistulas* and *rectal strictures* The latter may develop slowly and insidiously over a period of many years and are characterized by discharge from the bowel alternating constipation and diarrhea and eventual symptoms of partial obstruction Elephantiasis of the genitalia due to lymphatic obstruction is said to be common in the tropics but is rarely seen in this country Lymphopathia venereum is characterized by hyperproteinemia due to elevation of the serum globulin

Death rarely results from the lymphadenitis unless severe bacterial infection is superimposed Advanced cases of rectal stricture however have a poor prognosis

Diagnosis—The diagnosis of lymphopathia venereum is established definitely by means of the Frei test The condition is easily confused with syphilis chancroid and granuloma inguinale even by the expert In *syphilis* aspiration of the lymph node in the early phase should yield darkfield evidences of the invasive spirochete (p 45) *chancroid* is distinguished by the presence of the Ducrey bacillus in smears made directly from the genital ulcer in *granuloma inguinale* the Donovan bodies are demonstrable in smears made from exudate or biopsy The wise pract[illegible]

CHAPTER 24

THE MYCOSES

Fungous Infections of the Skin
Systemic Mycoses
- Actinomycosis
- Blastomycosis
- Sporotrichosis
- Torulosis
- Aspergillosis
- Coccidioidomycosis
- Moniliasis
- Histoplasmosis
- Geotrichosis
- Penicilliosis
- Rhinosporidiosis

FUNGOUS INFECTIONS OF THE SKIN

Chromoblastomycosis (*Hormodendrum pedrosoi*) (p 3316)
Erythrasma (*Microsporon minutissimum*) (p 3301)
Favus (*Achorion schoenleinii*) (p 3304)
Maduromycosis (Mycetoma, Actinomyces) (p 3315)
Moniliasis (*Monilia albicans*) (p 3301)
Paracoccidioidal Granuloma (Almeida's Disease) (*Paracoccidioides brasiliensis*) (p 3314)
Ringworm of the Auditory Canal (Aspergillus or Monilia) (p [illegible])
Ringworm of the Axilla (Actinomyces) (p 3305)
Ringworm of the Beard (*Microsporon lanosum or trichophyton*) (p 3304)
Ringworm of the Body (Microsporon trichophyton) (p 329)
Ringworm of the Feet (*Trichophyton gypseum or purpureum*) (p 3298)
Ringworm of the Groin (*Epidermophyton inguinale*) (p 3295)
Ringworm of the Nails (*Monilia albicans Achorion schoenleinii or trichophyton*) (p 3304)
Ringworm of the Scalp (*Microsporon lanosum or audouini*) (p 3302)
Tinea Imbricata (Endodermophyton) (p 330)
Tinea Versicolor (Chromophytosis) (*Microsporon furfur*) (p 3300)

SYSTEMIC MYCOSES

Systemic fungous involvements are noted in actinomycosis blastomycosis sporotrichosis torulosis aspergillosis coccidioidomycosis moniliasis histoplasmosis geotrichosis penicilliosis and rhinosporidiosis

ACTINOMYCOSIS
(*Streptothricosis Nocardiosis*)

Actinomycosis belongs to the group of infectious granulomas It is caused by several species of fungi of which *Actinomyces bovis* (the ray fungus) is most important The lesions which may be local or generalized are characterized by the formation of abundant granulation tissue that forms hard indurated masses of multiple abscesses which discharge the sulfur granules made up of pus and colonies of the fungus

Etiology — *Actinomyces bovis* is a parasite found in the lesions of man and animals It is gram positive, nonmotile, and nonacid fast. In the animal body the fungi appear as

in infected humans at autopsy intercellular inclusion bodies known as L C L are demonstrable in Giemsa stained sections These structures named after Leventhal Cole and Lillie are tiny ovoid or spherical bodies which usually appear in the cytoplasm of the mononuclears and also lie free in the intercellular spaces They are regarded as elementary virus particles

Etiology—The psittacosis virus is infectious for a variety of laboratory animals includ ing mice monkeys and Java rice birds It can be cultivated on the chorio-allantoic mem branes of developing chick embryos Infected birds and humans develop complement fixing antibodies during convalescence

Epidemiology—Psittacosis was first imported into the United States with a shipment of infected Brazilian parrots Since that time it has become apparent that the disease occurs also in parakeets that are bred in this country especially in California The infected birds are not necessarily ill the majority may be healthy carriers The virus is excreted in droppings urine and nasal mucus Air borne transmission to man is the most likely mechan ism since human infection has resulted from very brief contact with birds There is little doubt that beyond parrots and parakeets other exotic birds such as love birds may also carry the infection which does not differ greatly from ornitho is next to be described

Clinical Manifestations—The most striking clinical manifestations of human psittacosis are those of a *pneumonitis* (p 2188) It is only by the history of exposure to infected birds that the diagnosis is suggested since the clinical course may in most respects resemble other varieties of pneu monitis such as occur in influenza

The incubation period of human psittacosis varies from seven to four teen days The onset is usually fairly acute with a typhoid like syndrome consisting of malaise fever, headache nose bleeds photophobia chilliness backache anorexia nausea and vomiting Chills may occur at the onset or during the course of the illness muscle pains and backache are frequently encountered

Despite the fact that pathological manifestations are not observed at autopsy in psittacosis digestive disturbances are common They include nausea vomiting obstinate constipation intestinal distention and metero ism The spleen is not palpable Rose spots resembling those of typhoid fever have been occasionally noted The leukocyte count remains normal in every respect See *Differential Diagnosis of Commoner Febrile Intra thoracic Disorders* (p 404)

Diagnosis—The diagnosis of psittacosis is suspected only when there is a clear history of contact with parrots parakeets or other exotic birds The practitioner recalls that it is not necessary that the bird be actually sick since it may be a healthy carrier A positive diagnosis requires special tests which can be performed only by public health officials with fully equipped laboratories The sputum contains the virus when injected into mice death is produced with a characteristic lesion in which the L C L bodies are demonstrable a complement fixation test becomes positive in the patient s serum on or about the sixth to ninth day of the illness with a rising titer for several months

Prognosis—The case fatality rate of demonstrable psittacosis approaches 20 per cent Undoubtedly the vast majority of mild infections are not recognized Hence this figure may be deceptive

Treatment—Thus far there is no specific treatment for psittacosis Con valescent serum has been used but its availability is limited The sulfona

When the process in the skin is secondary to visceral involvement it manifests itself in the form of deep seated subcutaneous tumors which are firm to the touch The overlying skin is red or purple in color Fluctuation develops and eventually fistulous tracts discharging pus are present The surrounding skin is infiltrated and has a boardlike woody feel

Lumpy Jaw —See *Diseases of the Oropharynx* (p 1697)

Actinomycosis of the Tongue —Actinomycosis of the tongue begins as a deep seated nodule which gradually enlarges under the mucous membrane Eventually it ruptures and discharges pus but the process is soon repeated in adjacent areas until the tongue and the floor of the mouth become so thickened and indurated that the tongue cannot be protruded *Syphilis* and *cancer* must be distinguished from this type of actinomycosis by microscopic examinations and biopsy



Fig 77 —Actinomycosis of right upper lobe

Actinomycosis of the Lungs —The lungs may be involved by direct extension upward through the diaphragm by direct inhalation of fungi or by hematogenous metastasis The lesions may primarily involve the bronchi extend into the pulmonary tissue producing a fibrosing and excavating lesion or they may extend to the pleural cavity and through the chest wall The signs and symptoms resemble *tuberculosis* and systemic symptoms of cough fever sweats and weight loss are produced The radiographic appearance may suggest tuberculosis *lung abscess bronchiectasis or carcinoma of the lung* The only certain method of diagnosis is the demonstration of the fungus in the sputum or in the discharges through the chest wall See *Differential Diagnosis of Commoner Febrile Intrathoracic Disorders* (p 404)

Conant Martin Smith Baker and Callaway Manual of Clinical Mycology

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Treatment —Thus far there is no specific treatment for psittacosis Convalescent serum has been used but its availability is limited The sulfona

lin however there is very little doubt that the actinomyces are susceptible to the remedy and this preparation would definitely seem to be the therapeutic measure of choice reserving sulfonamide for the management of the penicillin resistant infections

Adequate and radical surgical drainage is essential with excision of pathological tissue Even pneumonectomy may be necessary Best results are obtained when surgery penicillin sulfadiazine and iodides are combined Vaccine therapy may be tried if this routine fails

BLASTOMYCOSIS

Blastomycosis is an infectious disease characterized by the formation of granulomas and miliary abscesses in the skin lungs and other viscera Several hundred cases have now been reported from many countries in the world North American blastomycosis is known also as Gilchrist s disease the South American variety is termed paracoccidioidal granuloma and Lutz Splendore Almeida s Disease

Etiology.—The disease is produced by several varieties of blastomyces which are morphologically identical but can be distinguished by cultural differences The organisms are best observed by mixing a drop of pus from a lesion with a few drops of 10 to 0 per cent solution of potassium hydroxide and examining the preparation under the microscope The fungi appear as round or oval highly refractile bodies varying in size from 5 to 20 μ containing granules and vacuoles and surrounded by a hyaline capsule Budding forms are seen as well as organisms in pairs forming a figure 8 See Fig

Blastomyces grow readily at room or incubator temperature on glucose agar where colonies resemble those of *Staphylococcus albus* In culture (but not in pus from lesions) the organisms develop branching hyphae and spores

Blastomyces are widely distributed in nature and may be cultivated from vegetation of all kinds Despite much speculation there is no definite knowledge as to the manner or portal of entry by which man is infected Males are more often affected than females and all ages appear susceptible The fungus is highly pathogenic for white mice less so for other laboratory animals

Pathology.—The pathological features of blastomycosis bear a strong resemblance in many respects to tuberculosis In the skin the lesions consist of pustules nodules gummatous lesions and ulcers in the viscera miliary or larger sized abscesses and nodules are produced The nodule of blastomycosis consists of a central necrotic mass containing the fungi polymorphonuclear leukocytes and debris Surrounding this are multinuclear giant cells of the Langerhans type identical with those present in tubercles Many of these giant cells contain ingested blastomyces On the periphery of the lesion are small round cells and granulation tissue

CLINICAL MANIFESTATIONS

Blastomycotic infections appear as cutaneous or systemic lesions The skin may be involved primarily in which case the disease is essentially benign as far as mortality is concerned and of an indolent and slowly progressive character In the systemic type of disease the lungs are almost always involved and the skin is affected as a result of hematogenous or lymphatic dissemination of the organisms In general about two thirds of all cases are primary in the skin and remain localized in that organ while one third are systemic involving the lungs primarily although no organ in the body is exempt

Primary Cutaneous Blastomycosis.—In the primary cutaneous type of blastomycosis the initial involvement is in the epidermis The lesions may begin as *papules* or *pustules* which rupture and form overlying crusts The lesion spreads peripherally and may eventually involve large areas of skin

is far from clear Originally they were regarded as a variety of protozoa at present they are thought to be bacterial It has been claimed that they are gram negative encapsulated bacilli related to Friedlander s bacillus No uniform success has attended efforts to cultivate these organisms They are not pathogenic for laboratory animals and it is doubtful whether human volunteers have been infected by injection See Fig 73

Clinical Manifestations —The infection occurs in both sexes as a result of *sexual intercourse* The *incubation period* is variable The earliest lesion is a *nodule* on the penis or labia minora The primary infection gradually extends over the skin and mucous membranes As the process extends the epidermis rubs off leaving a granulomatous and excoriated surface The lesion rarely is deeply penetrating but may be very extensive The process involves the groin the inner aspects of the thighs and the mucous mem

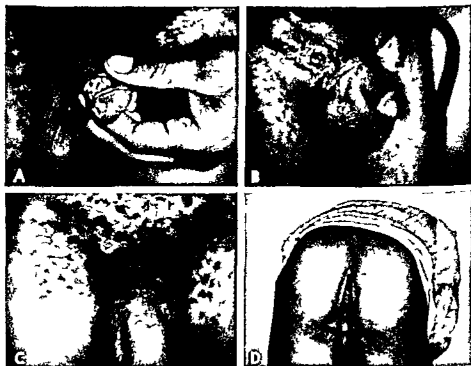


Fig 74—Granuloma inguinale Lesions of penis groins and anu

brane of the vagina so that rectovaginal fistula may result Healing *with scarring often goes on in one area while the lesion* advances in another The process is characterized by its great indolence and chronicity There are no constitutional symptoms The regional lymph nodes are uninvolved unless secondary bacterial infection occurs

Diagnosis —The diagnosis of granuloma inguinale is made by obtaining scrapings from the lesion staining them with Wright s or Giemsa s stain and examining for the characteristic encapsulated coccoid or rodlike intracellular *Donovan bodies* *Lymphopathia venereum* *chancroid* and *syphilis* are differentiated on clinical grounds and by appropriate laboratory tests *Epidermoid carcinoma* (*epithelioma*) may sometimes be confused but the slow course of granuloma inguinale serves to distinguish it

nary involvement is most often seen The disease is generally primary in the *lungs* probably as a result of inhalation of organisms The initial lesion is in the bronchi following which bronchopneumonia develops The onset may be acute or insidious There may be a dull pleural pain and bloodtinged sputum

Constitutional symptoms consist of fever sweats emaciation cough sputum and chest pain The early pulmonary lesion is *pneumonic* in type but *abscess* and *granuloma formation* take place as chronicity is established Unless the characteristic skin lesions are also present the distinction between this disease and pulmonary tuberculosis is difficult except by careful examination of the sputum The prognosis of the pulmonary form of the disease is quite poor It is stated that 90 per cent of the cases terminate fatally within three years Bone infection occurs in 60 per cent of systemic forms vertebrae and ribs being most often affected (Fig 78)

See *Differential Diagnosis of Commoner Febrile Intrathoracic Disorders* (p 404)

DIAGNOSIS

Besides demonstration of the fungus systemic infection may be diagnosed by a positive skin response to blastomyces vaccine or a positive complement fixation test on serum

TREATMENT

There is no satisfactory specific treatment for this disease If the skin lesion is small and localized (the primary cutaneous type) *surgical excision* may be feasible or curettage and cauterization may be done *Radium* and *roentgen therapy* have also been used but most reliance is placed on the *iodides* These are given in doses as large as can be tolerated *Sulfonamide* drugs warrant a trial in conjunction with iodide but penicillin seems ineffectual Vaccine desensitization may be tried in conjunction with iodide and roentgen therapy

SPOROTRICHOSIS

Sporotrichosis is a chronic infectious disease caused by several varieties of the fungi of the genus Sporotrichum and characterized by chronic granulomatous gumma like lesions of the skin and subcutaneous tissues Visceral involvement is rare

Etiology—The etiological agents are filamentous spore-bearing *fungi* A number of different varieties have been noted but it is doubtful whether there are any essential differences among them These fungi grow aerobically at room temperature on Sabouraud s medium Microscopic examination of cultures reveals a tangled mass of fine branched septate mycelia. The spores which are about 3 to 6 μ long, are pear-shaped and are situated along the length of the filaments In preparations of pus obtained from lesions the fungus can rarely be demonstrated and the diagnosis must be made by culture rather than by direct examination of smears The sporotricha are pathogenic for most laboratory and domestic animals The disease occurs spontaneously in rats dogs and horse

Sporotricha are common saprophytes in plant life of all sorts They are present in all types of soil and at all latitudes and survive indefinitely under the most adverse conditions Man is probably most commonly infected by the direct introduction of organisms into broken skin Since certain insects may carry the fungus the bite of flies ants or wasps may introduce the infective organism The bite of rats and man to-man transmission by contact with the lesions of infected persons have also been reported The disease has been observed in most

and *dengue fever* which is also transmitted by the bite of this mosquito is common in the Orient. It is difficult to explain why yellow fever is not present also in this area.

Immunity.—Natural immunity to yellow fever is either uncommon or nonexistent. In endemic areas most inhabitants including children have acquired *active immunity* as a result of previous infection. The disease may have been so mild as to be clinically unrecognizable. These facts are known today because of new epidemiological tools. One of these is the *viscerotomy* technic which consists of obtaining a piece of liver from all persons dying in endemic areas and subjecting the biopsy specimen to histological examination for the typical pathological evidence of yellow fever. The other technic is the test for *virus neutralizing antibodies* in the blood of residents in endemic areas. Persons who have active immunity as a result of previous infection have antibodies in the blood which when mixed with virus protect mice from otherwise fatal infections. It is by means of *surveys* using these technics that the present prevalence of jungle yellow fever has become apparent.

Pathology.—The most striking changes are found in the *liver*. Grossly that organ is normal in size and only slightly pale in color but histological examination discloses an extensive necrosis of the liver cells with the destruction of the lobules most marked in the midzonal regions and extending toward the periphery. In extreme instances 95 per cent of the hepatic cells are destroyed by a process which is essentially degenerative rather than inflammatory. Peculiar acidophilic staining hyaline masses are described in the liver. For those who have had experience with the disease the histological appearance of the liver is pathognomonic of yellow fever (Councilman bodies).

The *kidneys* are also the site of degenerative changes which vary from cloudy swelling to severe necrosis especially in the cells of the convoluted tubules but involving the glomerular tufts as well. Degenerative changes are found in all parts of the *myocardium* including the conduction system. They explain the clinical findings of bradycardia, low blood pressure and venous stasis as well as the alterations in the electrocardiographic tracing.

An outstanding feature of the disease is hemorrhage from the mucous membranes of the intestinal tract and from the serous surfaces. The stomach is filled with altered blood producing the *black vomitus* characteristic of the severest type of yellow fever. Petechial hemorrhages are also seen on serous surfaces of the heart and pleural cavity as well as in the skin and lungs.

Biochemical disturbances which are the result of hepatic insufficiency can be detected in the blood of the more severely ill patients and the degree of abnormality is an index to prognosis. Early changes include increased serum bilirubin, decreased fibrinogen and impairment of hepatic function as measured by dye excretion. Later in the course of the disease hypoglycemia, elevation of nonprotein nitrogen, especially amino-acid nitrogen and elevation of blood guanidine indicate that a severe degree of hepatic insufficiency exists.

Clinical Manifestations

The *incubation period* of yellow fever varies from three to six days. The onset is abrupt with symptoms of headache, malaise, backache, pains in the legs, nausea and vomiting. The temperature and pulse rate mount rapidly, reaching their maximum by the end of the first twenty four hours and then decline. The pulse rate falls more rapidly than the temperature so that a relative bradycardia results. Thereafter the pulse remains slow although there may be a secondary elevation of temperature. Heavy *albuminuria* is commonly present in the early stages. It is of diagnostic value but does not necessarily indicate that renal insufficiency will develop.

By the end of the second or third day of illness the temperature has returned to normal and the initial symptoms have abated. Then from the third to the fifth day of the disease the entire clinical picture changes. The patient again becomes critically ill and develops the full manifestations of the disease. These include nausea, vomiting, falling blood pressure and the ominous signs of *jaundice*, *hemorrhage* and *diminishing urinary output*. The jaundice is commonly subicteric and is rarely heavy. Nausea and vomiting are intractable leading to hematemesis which may be severe.

nary involvement is most often seen The disease is generally primary in the *lungs* probably as a result of inhalation of organisms The initial lesion is in the bronchi following which bronchopneumonia develops The onset may be acute or insidious There may be a dull pleural pain and bloodtinged sputum

Constitutional symptoms consist of fever sweats emaciation cough sputum and chest pain The early pulmonary lesion is *pneumonic* in type but *abscess* and *granuloma formation* take place as chronicity is estab lished Unless the characteristic skin lesions are also present the dis tinction between this disease and pulmonary tuberculosis is difficult except by careful examination of the sputum The prognosis of the pulmonary form of the disease is quite poor It is stated that 90 per cent of the cases terminate fatally within three years Bone infection occurs in 60 per cent of systemic forms vertebrae and ribs being most often affected (Fig 78)

See *Differential Diagnosis of Commoner Febrile Intrathoracic Dis orders* (p 404)

DIAGNOSIS

Besides demonstration of the fungus systemic infection may be diag nosed by a positive skin response to blastomyces vaccine or a positive complement fixation test on serum

TREATMENT

There is no satisfactory specific treatment for this disease If the skin lesion is small and localized (the primary cutaneous type) *surgical excision* may be feasible or curettage and cauterization may be done *Radium* and *roentgen therapy* have also been used but most reliance is placed on the *iodides* These are given in doses as large as can be tolerated *Sulfona mide* drugs warrant a trial in conjunction with iodide but penicillin seems ineffectual Vaccine desensitization may be tried in conjunction with iodide and roentgen therapy

SPOROTRICHOSIS

Sporotrichosis is a chronic infectious disease caused by several varieties of the fungi of the genus Sporotrichum and characterized by chronic granulomatous gumma like lesions of the skin and subcutaneous tissues Visceral involvement is rare

Etiology—The etiological agents are filamentous spore bearing *fungi* A number of different varieties have been noted but it is doubtful whether there are any essential *differences* among them These fungi grow aerobically at room temperature on Sabouraud s medium Microscopic examination of cultures reveals a tangled mass of fine branched septate mycelia The spores which are about 3 to 6 μ long are pear shaped and are situated along the length of the filaments In preparations of pus obtained from lesions the fungus can rarely be demonstrated and the diagnosis must be made by culture rather than by direct examination of smears The sporotricha are pathogenic for most laboratory and domestic animals The disease occurs spontaneously in rats dogs and horses

Sporotricha are common saprophytes in plant life of all sorts They are present in all types of soil and at all latitudes and survive indefinitely under the most adverse conditions Man is probably most commonly infected by the direct introduction of organisms into broken skin Since certain insects may carry the fungus the bite of flies ants or wasps may introduce the infective organism The bite of rats and man to-man transmission by contact with the lesions of infected persons have also been reported The disease has been observed in most

For vaccination 0 5 cc of the dehydrated virus is injected subcutaneously Immediately before use the virus is mixed in the proportion of 1 to 10 parts of sterile saline and the injection is made within three hours of dilution In an endemic area a booster dose of 0.5 cc is given every two years in the presence of an epidemic the booster dose is given immediately although it appears that the duration of immunity following yellow fever vaccine may be as long as two to four years

Aside from the homologous serum jaundice (p 82) to which reference has been previously made there are few reactions to yellow fever immunization

Treatment

Despite increasing knowledge of yellow fever the treatment of the disease is still ineffective and disappointing The anti infective agents appear ineffectual but penicillin is worthy of trial in desperation Fluids containing dextrose are given parenterally Calcium salts and vitamin K may be added to the symptomatic routine using 10 to 20 cc of 7 5 per cent calcium gluconate and 1 to 2 mg of menadione each day

SANDFLY FEVER (THREE DAY FEVER PAPPATACI FEVER)

Sandfly fever is also known under the names of phlebotomus fever pappataci fever three day fever Mediterranean dengue summer influenza summer fever Hundskrankheit soldaten fieber acclimatization fever endemic or climatic gastro enteritis and Chitral fever

Sandfly fever is a virus disease the vector is the night biting sandfly *Phlebotomus pappataci* The disease occurs in tropical and subtropical regions that are indigenous to the vector Many American soldiers on duty in the Mediterranean bases became afflicted in both the World Wars Natives are apparently immune probably as the result of a previous attack and the development of some protective mechanism

Clinical Manifestations—The clinical picture of sandfly fever resembles an influenza without the respiratory symptoms The temperature may range from 100 to 105 degrees F with headache pains in the eyes back muscles bones and joints subjective stiffness of the neck photophobia and occasional attacks of nausea vomiting abdominal distress constipation or diarrhea

The fever usually lasts three days but convalescence is prolonged for another ten days due to more than moderate depletion

Treatment—The treatment of sandfly fever is symptomatic The patient is given liberal doses of *analgesics* during the day and may require an *opiate* during the night A *vaccine* prepared from the virus and irradiated by ultraviolet ray is capable of producing immunity without giving rise to the disease More important however is prevention through the use of sandfly repellents the most successful of these being vanishing cream containing *dimethyl phthalate* and *pyrethrum*

MUMPS (EPIDEMIC PAROTITIS)

Mumps is an acute communicable disease characterized by nonsuppurative swelling and pain in the parotid and other salivary glands Ordinarily a benign disease complications such as meningo encephalitis

Synonyms.—Torulosis is known also as cryptococcosis European blastomycosis and *Busse-Buschke's disease The causative organism may be referred to as Cryptococcus neoformans* or *Torula histolytica*

Etiology—Torula is a *yeast* which reproduces by budding without mycelia or endospore formation It is widely distributed on plants where it seems to be saprophytic The organisms are ovoid, spherical cells, 3 to 15 μ in diameter enclosed by a definite cell wall In sputum pus or spinal fluid they may closely resemble lymphocytes With Wright's stain *the nucleus and cytoplasm of the white cell are clearly apparent whereas the structure of* Torula remains undifferentiated On artificial media, the parasites grow readily under aerobic conditions at room or body temperature Torula is pathogenic for most laboratory animals and the laboratory diagnosis should include culture and animal inoculation

The method of human infection is not known and the portal of entry is equally obscure It is commonly believed that the organisms gain entrance to the body through the respiratory tract *If this is so it is hard to see why central nervous system involvement regularly* occurs whereas the lungs are involved in only 40 per cent of the cases



Fig 9—Cryptococcosis of the lungs Lesions disappeared after prolonged treatment with *sulfadiazine*

Pathology—In the *pulmonary type* of the disease the lesion consists of small tubercles. In the *cerebrospinal type* the picture is that of chronic leptomeningitis with a thickening and matting of the membranes Very little exudation is present but tubercles may be scattered throughout the involved tissues Microscopically in the brain substance Torula organisms *are surrounded by a gelatinous material.* There is very little *cellular* reaction to the invading parasites Moderate leukocytosis is usually present.

Clinical Manifestations—Cerebrospinal torulosis is characterized by insidious onset with *marked headache* and *dizziness* There is generally *fever* and *tachycardia* Visual disturbances are common and may consist *of diplopia nystagmus* and *failing vision Confusion drowsiness aphasia cerebral palsies* and *hemiplegias* have been described

Courtesy of Dr E E Menefee.

Such symptoms include *headache malaise nausea vomiting* and *elevation of temperature* which may reach 104° F In milder cases the temperature rarely goes above 102° F and local symptoms are the first evidence of the disease

The *parotitis* is noted by tenderness just behind the angle of the jaw The pain increases and swelling of the parotid soon follows The parotid *glands are involved in the vast majority of cases and one gland is usually* involved a day or two before the other Bilateral involvement occurs in 70 per cent of patients The swelling increases rapidly reaching its maximum on the third day remaining stationary for two or three days and slowly subsiding by the end of a week The degree of swelling varies In severe cases the patient s face may be distorted beyond recognition The swelling is chiefly in front of the ear extending onto the face and from the angle of the jaw to the zygomatic arch It also extends behind and below the ear so that the ear lobe is in the center of the swollen area

Involvement of the *submaxillary glands* occurs in about 10 per cent of patients Sometimes the sublingual glands on the floor of the mouth are also affected

Fever lasts generally for three or four days in uncomplicated cases The gland is tender to touch and movement of the jaws causes pain Salivation is decreased and the mouth is dry The tasting of acid foods aggravates the pain only if the parotid duct is obstructed by edema hence the popular test is of little diagnostic significance A helpful diagnostic feature however is the swelling and redness surrounding the mouth of *Stensen s duct* situated on the buccal mucosa opposite the second upper molar teeth

Complications

In children before the age of puberty complications are uncommon In adolescents and adults however they are frequent and may be serious They include *orchitis oophoritis mastitis pancreatitis meningitis* and other neurological disorders

Orchitis —Orchitis occurs in from 5 to 25 per cent of male patients past puberty It has long been felt that trauma favors localization of the infection in the gonads but there is little evidence to support this view The incidence of orchitis during mumps is in fact as high among infantry troops as in *the horse cavalry Orchitis may precede parotid swelling or occur as* the only manifestation of mumps but most often it develops during the second week after the onset of parotitis The swelling comes on rapidly and may be accompanied by chills high fever and excruciating pain due to the distention of the gland beneath the tense and unyielding tunica albuginea The body of the testicle is more commonly involved than the epididymis Hydrocele and edema of the scrotum often accompany the involvement of the testes Bilateral orchitis is unusual but swelling of one side may follow the other Acute swelling subsides in a week in all but the most severe cases Atrophy of the involved testicle occurs in about half of the more severe cases if untreated On the other hand enough functioning tissue remains so that even in the presence of bilateral involvement *sterility* is uncommon

Mastitis —Swelling and tenderness of the breast tissue may occur in both sexes but it is rarely troublesome

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Courtesy of Dr E. E. Menefee.

and especially in military establishments On the other hand aside from the difficulty of obtaining convalescent serum one may well question the need for its administration to exposed susceptible children In them the disease is mild and of a benign nature with few serious complications If the disease is temporarily prevented in childhood the patient remains susceptible and the time of his eventual attack is merely postponed to an older age when the incidence of serious complications is greatly increased

Treatment

There is no satisfactory evidence that convalescent serum administered after the onset of symptoms modifies the course or severity of the disease or the frequency of complications

Mumps is self limited and only symptomatic treatment is required The patient should be put to bed during the febrile period For the relief of parotid pain hot or cold applications may be used depending on which affords most relief for the patient The diet should be fluid in the acute stage since mastication increases the pain

The treatment of mastitis oophoritis and pancreatitis is symptomatic *Orchitis* in most cases is not severe It should be treated by bed rest and mechanical support of the inflamed testicle by a suspensory and thigh bridge If the testicle becomes very hard and tense and is accompanied by extreme pain chills and high fever immediate surgical incision for the relief of pressure is indicated This should be done under general anesthesia making a cruciate incision in the tunica albuginea mere incision and drainage of the hydrocele fluid is not enough The operation should be reserved for the severest cases but if it is performed promptly subsequent atrophy of the testicle will be prevented in a high percentage of cases

Mumps meningitis can be treated only symptomatically When signs of meningeal irritation develop lumbar puncture should be done for diagnostic purposes If the fluid is bacteriologically sterile and does not have the characteristics of a pyogenic meningitis (p 213) subsequent lumbar punctures are not necessary unless indicated to relieve symptoms of increased intracranial pressure

REITER S DISEASE

A distinct clinical entity characterized by an attack of diarrhea and followed by the triad of urethritis polyarthritis and conjunctivitis has been recognized by Reiter

The affliction appears to be a virus infection It is resistant to antibiotic therapy in contradistinction to gonorrhea which it resembles closely

Reiter s disease is non venereal It may be complicated by cystitis balanitis keratitis and iritis Signs persist for many weeks but eventually disappear usually without permanent sequels

In endemic areas of Arizona and California many persons with positive coccidioidin skin tests and negative tuberculin reactions have *calcified pulmonary nodules* indistinguishable from healed Ghon tubercles (p 256)

Cavitation has been reported so that the roentgenograph may be indistinguishable from tuberculosis unless sputum or gastric washings are examined for both tubercle bacilli and coccidioides Patients may have repeated small *hemoptyses* over a period of years yet the lesion does not necessarily progress and the cavity remains thinwalled Localized areas of *bronchiectasis* may develop in the course of pulmonary coccidioidal infection *Pleural effusions* have also been reported and *Coccidioides immitis* has been recovered in the fluid *Eosinophilia erythema nodosum* and other types of erythematous eruptions are not constant features but are frequently seen Relatively few patients have died in this stage Recovery is generally complete in a few weeks or a few months unless cavitation or bronchiectasis occurs

See *Differential Diagnosis of Commoner Febrile Intrathoracic Disorders* (p 404)

Chronic Coccidioidomycosis—Some patients and the frequency is not known do not recover completely from the initial illness but develop a progressive pulmonary infection with hematogenous dissemination to other tissues of the body The case fatality rate of this chronic type of coccidioidomycosis is 50 per cent In the skin and subcutaneous tissues abscesses and gumma like lesions develop Osteomyelitis arthritis and involvement of the pelvic organs have been reported The joint manifestations may be prominent and are often labeled desert rheumatism In rare cases the central nervous system or spinal cord shows gummatous lesions or abscesses *The course of the generalized type of disease is progressively* downhill and death follows in a few months or in several years

See *Differential Diagnosis of Commoner Febrile Skeletal Disorders* (p 192)

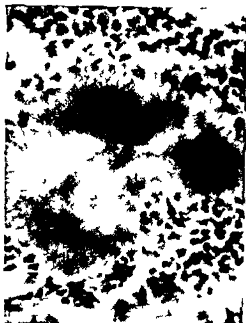
DIAGNOSIS

The diagnosis is made with certainty by the isolation and identification of *Coccidioides immitis* Clinically *pulmonary tuberculosis* can be confused with both acute and chronic types of pulmonary involvement The transient pulmonic infiltrations of the primary infection with *Coccidioides immitis* together with the grippe like symptoms which accompany them are not unlike instances of *atypical pneumonia of unknown etiology* (p 400) The skin lesions may be confused with *syphilitic gummas* or other types of *mycotic infection*

Smears and Cultures—The organisms may be identified in sputum gastric washings or in pus aspirated from cutaneous lesions Such materials should be concentrated by the addition of 10 to 20 per cent potassium hydroxide followed by centrifugation The sediment should then be examined unstained under the microscope for the presence of oval refractile yeastlike bodies At the same time a portion of the concentrated sediment is cultured on Sabouraud s medium and guinea pigs are injected intraperitoneally and intratesticularly From ten to thirty days later abscesses develop in the viscera of these animals from which the organisms can be isolated in pure culture

Skin Test with Coccidioidin—The intradermal skin test with coccidi

on a slide and 1 or 2 drops of water or 10 or 20 per cent sodium or potassium hydroxide are added The area is outlined with vaseline and a cover slip is carefully placed on top



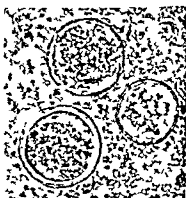
A



B



C



D

Fig 75—Mycoses *A* Actinomycosis Sulfur granules in pus from sinus tract *B* Blastomycoses Budding yeast like cells in tissue section *C Torula histolytica* Budding *forms in spinal fluid* † *D* Coccidioidomycosis From pus aspirated from lymph node.‡

If the preparation is gently heated over a low Bunsen burner or an alcohol lamp *clearing is immediate and examination may be carried out* directly Otherwise twelve to twenty four hours should elapse before microscopy

Mackie Hunter and Worth Manual of Tropical Medicine
† Johns and Attaway Am J Clin Path Vol III
‡ Stiles and Davis J.A.M.A., July 4 1942

in patients whose dentures are ill fitted In addition to bronchial and pul monary mycosis monilia may also cause septicemia endocarditis and meningitis

Cutaneous Moniliasis —The cutaneous forms of moniliasis are discussed elsewhere (p 3301)

Thrush —Thrush is a form of *stomatitis* characterized by the appear ance on the mucous membranes of the mouth of small white flakes or larger patches In these lesions monilia may be identified The spores lodge between the epithelial cells and separate them Then the growth pene trates the deeper structures and also spreads along the mucosal surface The inside of the lips and cheeks the margin of the tongue and the hard palate are commonly involved but sometimes the tonsils and pharynx

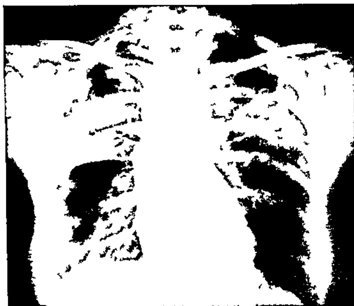


Fig 81 —Moniliasis of the lungs

also may be covered with white patches The lesions are usually situated on an erythematous base and when removed leave bleeding points

The *diagnosis* is generally not difficult and is readily confirmed by examination of the scrapings under the microscope Syphilitic mucous patches should rarely be confusing Vincent s infection and diphtheria are both acute infections with constitutional symptoms whereas there are practically no symptoms except dryness of the mouth associated with thrush

The *treatment* is simple and consists in the application of 1 per cent *aqueous gentian violet solution* several times a day or of 10 per cent oint ment or powder of the sodium salt of caprylic acid several times daily

Pulmonary Moniliasis —Pulmonary moniliasis is a rare condition which may be confined to the bronchi producing symptoms of chronic bronchitis or bronchiectasis or may involve lung tissue proper In the latter case the

Conant, Martin Smith Baker and Callaway Manual of Clinical Mycology

The Stained Smear—The practitioner, unless he is very expert should not rely upon direct microscopy Smeared preparations should be prepared from exudate pus or fresh bits of tissue and stained by the methods of Giemsa and Wright for submission to the mycologist

Cultivation—The cultivation of fungi requires most expert technical assistance and is usually practiced upon the Sabouraud maltose agar media whose *p*H has been corrected to between 5 and 6 Since growth is slow the culture tube must be retained for at least one week The report may be considerably delayed to the great annoyance of both practitioner and patient

Animal Inoculation and Skin Test—The pathogenicity of an isolated fungus may be tested on mice guinea pigs or rabbits using intracutaneous subcutaneous intravenous or intraperitoneal injections Additionally antigens prepared from coccidioides trichophyton and epidermophyton are *available for clinical use*

CLINICAL MANIFESTATIONS

Histoplasmosis generally appears as a systemic febrile disease characterized by *large liver and spleen anemia* and *leukopenia* In some of the cases chronic pulmonary symptoms or manifestations of ulcerative enterocolitis have been prominent

Infants less than 2 years of age make up 20 per cent of reported cases In the young lymphadenopathy is marked bone marrow involvement is extensive and purpura may be noted Extensive pharyngeal and laryngeal lesions may be observed and pulmonary or osseous complications inevitably ensue (Fig 89) It is possible that dogs and other domestic pets transmit the disease

DIAGNOSIS

In only a few cases has histoplasmosis been diagnosed antemortem It should be suspected in febrile systemic diseases characterized by a multiplicity of organ involvement The diagnosis is made by finding *phagocytized parasites in blood smears* or in tissue obtained by biopsy of lymph nodes bone marrow or spleen It has been suggested that in cases of enteritis the organisms may be excreted in the stools Recently a specific skin test has been developed which may prove of diagnostic value

TREATMENT

The reported cases have been fatal and no form of effective therapy has as yet been devised It has been suggested that pentavalent antimony preparations be tried (p 133)

GEOTRICHOSIS

Geotrichosis is a rare disease of fungous origin It involves the mouth especially producing white patches Intestinal bronchial and pulmonary lesions also have been reported

The diagnosis is established by direct examination of smears of exudate sputum or stool The organism appears as an oblong or rectangular cell The morphologic diagnosis must be corroborated by culture

Treatment is successfully carried out with gentian violet Accessible lesions are painted with a 1 per cent aqueous solution and intestinal disturbances may yield to salol coated capsules of the dye Bronchopulmonary infections respond to iodides and autogenous vaccine

PENICILLIOSIS

Penicilliosis is of importance chiefly because of its implications relative to the use of penicillin in anti infective therapy (p 109) It is of interest to note that this life saving fungus also may invade tissue and produce otomycosis (p 3305) or pulmonary abscess (p 2214)

RHINOSPORIDIOSIS

The *Rhinosporidium seeberi* may infect nose eyes ears larynx vagina penis and skin The characteristic lesion is a friable polyp It is seen in South America Persia Malay States India Ceylon and South Africa

The disease is rarely fatal and is treated by surgical dissection of the polyps and cautery of the bases Antimony in trivalent (p 133) or pentavalent forms may be tried

large rods with clubbed ends The fungus grows well under anaerobic conditions on 1 per cent glucose agar Nocardia asteroides is an aerobic partially acid fast variant

In the discharges from lesions actinomyces are present as characteristic *sulfur granules* seen with the naked eye For identification under the microscope a granule is placed on a glass slide to which is added a few drops of sodium or potassium hydroxide (15 per cent) A cover slip is applied with pressure so as to spread the material out in a thin film This preparation is examined unstained under the microscope A dense central zone of a compact mycelial reticulum an intermediate amorphous zone and an outer rim which is refractile striated and composed of *mycelial filaments or hyphae* are seen These hyphae are 10 to 20 μ in length with expanded clublike ends The radial arrangement of the clublike forms accounts for the name *ray fungus*

Pathology—The fungus gives rise to a *granulomatous reaction* in human or animal tissues In the early stages the lesion consists of a center of fungi and polymorphonuclear leukocytes surrounded by necrotic tissue and cell debris Beyond this there is a layer of granulation tissue Gradually the central purulent area becomes larger The pus tends to burrow through the tissues and eventually it reaches the skin forming multiple *fistulas* or *sinus tracts* which are indolent and discharge pus containing the granules of fungi The affected organ is gradually converted into a mass of granulation tissue tunnelled with sinus tracts and pockets of pus

Pathogenesis—There is considerable difference of opinion as to the natural habitat and the means by which actinomyces gain entrance to human tissues Actinomycosis is found throughout the world and the disease is by no means rare in the United States In 1923 Sanford collected 678 cases and thought that they represented only a small percentage of the actual number of the afflicted It was formerly thought the disease primarily affected persons in rural communities (especially those in intimate contact with cattle) and that man like cattle acquired the disease by chewing blades of glass and stalks of grain The newer point of view emphasizes that the natural habitat of the fungus is the buccal cavity and gastro-intestinal tract of man and animals The lowering of tissue resistance or local trauma allows the organisms to become pathogenic and thus the occasional development of actinomycosis of the jaw following tooth extraction in persons living in urban communities seems best explained

Although all ages are susceptible to actinomycosis the majority of cases occur in the twenty-to-forty year age group and nearly 80 per cent of the recorded cases have been males The peculiar age and sex distribution is not readily explained

CLINICAL MANIFESTATIONS

No tissue is exempt from involvement by actinomycosis but certain anatomical distributions of the infection are more common than others About 60 per cent of the cases occur on the head and neck and most of these are examples of so called *lumpy jaw* with involvement of the skin and subcutaneous tissue and destruction of the mandible The neck structures may be separately inflamed and 20 per cent of cases involve the abdominal wall or the abdominal viscera usually the appendix cecum or liver The lungs pleura and chest wall are affected in 15 per cent of the cases Rarer forms of the disease include inflammations of the ovaries and fallopian tubes urinary tract central nervous system and mediastinum

Cutaneous Type—Cutaneous involvement is occasionally primary but usually results from extension to the overlying skin of the granulomatous process from the mouth pharynx lungs pleura and abdominal organs

In the primary type of actinomycosis the process begins as a *nodule* in the epidermis which gradually extends down to involve all layers of the skin and subcutaneous tissues The lesion becomes fluctuant ruptures and discharges purulent material containing the yellow *sulfur granules* The nodule is finally converted into an indolent *ulcer* which may persist indefinitely or slowly heal with marked scarring

Flagellates (Mastigophora)

GIARDIA LAMBLIA

See *Giardiasis* (p 1892)

TRICHOMONAS VAGINALIS

See *Female Reproductive System* (p 2098)

Trichomonas hominis

Trichomonas elongata

TRYPANOSOMA

T GAMBIENSE

T RHODESIENSE

T CRUZI

See *Trypanosomiasis African Rhodesian and American Sleeping Sickness* (p 531)

LEISHMANIA

L DONOVANI

L TROPICA

L BRASILIENSIS

See *Systemic Leishmaniasis Kala Azar* (p 534)
Cutaneous Leishmaniasis (p 3319)

Ciliates

BALANTIDIUM COLI

See *Balantidiasis* (p 1893)

MALARIA
(*Paludism Ague*)

Malaria is one of the most widely prevalent diseases in the world In some regions it accounts for an appreciable proportion of all morbidity and mortality although it is uncommonly encountered in the northern temperate climates

The Malarial Parasite—Malaria is caused by infection with protozoan parasites of the genus Plasmodium The common species which infect man are *P vivax* *P malariae* and *P falciparum*

Life Cycle—The malarial parasites go through a complicated life cycle and require as hosts both man and the mosquito Man is the intermediate host in whom the *asexual cycle* takes place The mosquito is the definitive host in which the *sexual cycle* occurs

ASEXUAL CYCLE —The asexual or *schizogony cycle* begins in man when an infected mosquito bites and introduces the sporozoites into the human body The first visible malarial parasites are minute ringlike bodies lying upon or within the red blood cell These bodies or *trophozoites* enlarge develop pigment and divide into *schizonts* The schizonts increase until they almost fill the invaded blood cells and finally divide into a number of small *merozoites* which are liberated into the blood stream by the rupture of the infected red cells The free merozoites invade other red cells and the performance is then repeated The cycle takes forty eight hours for *P vivax* (tertian malaria) seventy two hours for *P malariae* (quartan malaria) and from thirty-six to forty-eight hours for *P falciparum* (estivo autumnal malaria)

SEXUAL CYCLE —After a variable number of asexual cycles some of the parasites become differentiated into sexual forms as male and female *gametocytes* The gametocytes differentiate up to a certain point in man but are unable to complete their life cycle unless they gain access to a particular species of mosquito

When the blood of a person containing gametocytes is ingested by a mosquito of the proper species the parasites undergo a sexual life cycle in the stomach of the insect and eventually *sporozoites* are liberated into the salivary ducts When another human victim is

Actinomycosis of the Abdominal Organs —The *cecum* and *appendix* are the commoner sites of abdominal involvement The onset may be acute in character simulating acute appendicitis but usually when the patient is seen a mass is palpable in the right lower quadrant If operation is performed a granulomatous induration of the tissues is seen The wound does not heal and eventually internal fistulas and sinuses develop These discharge pus containing the fungi

The *liver* may be involved by lymphatic or hematogenous spread and the *hip joint* may be destroyed by direct spread through fascial planes The *female genital organs kidneys* and *urinary bladder* have also been involved in reported cases

Rare cases occur in which the *brain* and *spinal cord* are involved by localized abscesses or more diffusely This type of disease is usually fatal in short order

PROGNOSIS

Actinomycosis is essentially a chronic disease Its duration depends partly upon the organs involved The primary cutaneous type may last untreated for ten years whereas the cerebral type is usually fatal in a matter of weeks The type of disease involving the face and neck lasts several years while the pulmonary type is generally fatal within a year

DIAGNOSIS

The diagnosis of actinomycosis depends upon the identification of the ray fungus in the discharges from lesions When the disease involves the skin the diagnosis is readily made but when the viscera are involved diagnosis can only be suspected until at operation pus is obtained for study

Failure to find granules in a discharging sinus may be corrected by applying dry sterile gauze over the wound The next morning granules may be seen in the gauze Organized granules may not be present in sputum or spinal fluid hence stained smears should be examined for the presence of short branching gram positive or acid fast elements Absolute diagnosis can be made by biopsy only if the actinomycotic granule is found (p 486) Extracts of Nocardia may become useful as diagnostic skin testing material or as desensitizing agents

TREATMENT

In the past *roentgen therapy thymol* and *iodide* have been used in the treatment of this disease Some patients seem to have responded to this type of therapy while others were completely resistant

The *iodides* are given in large doses beginning with 10 or 15 drops of saturated solution of potassium iodide three times daily and gradually increasing the dosage up to the limit of tolerance which may be as high as 350 drops

A much more hopeful approach to the therapy of actinomycosis is through the medium of the anti infective agents Full therapeutic doses of *sulfonamides* given over long periods of time seem to produce a consistent if not dramatic improvement in the inflammatory process The duration of the response suggests that the effect of the sulfonamide was rather on the secondary invading organism than on the primary assailant With *penicil*

bitten the sporozoites are injected into his blood stream and the asexual cycle in man begins anew The life cycle in the mosquito takes from ten to fourteen days depending on variations in temperature and humidity

Morphology of Parasites—It is impossible to describe completely in a brief space the morphological appearance of the three species of malarial parasites at various stages in the life cycle The *ring forms* of tertian malaria are rather large and there is usually only one ring to a red cell In the estivo-autumnal form there may be several small rings in a cell Reddish staining granules (*Schüffner's dots*) are prominent in the tertian form which causes a great increase in the size of the infected red cells Quartan malaria does not enlarge the parasitized red cell and the asexual forms in this species tend to arrange themselves in a band across the red cell but do not completely fill it With both *P vivax* and *P malariae* the entire asexual cycle occurs in the peripheral capillaries so that all stages in the cycle *can be seen in blood smears* With *P falciparum* however only the early ring forms and the sexual gametocytes are seen in the peripheral blood stream as the intermediate stages of development go on in the visceral capillaries The gametocytes of *P falciparum* are *easily distinguished from those of the other two malarial species by their crescent or cigar shape* These features are best summarized on the charts prepared by the United States Naval Medical School (Table 28)

Epidemiology—*The malarial parasites of man are transmitted by various species of Anopheles mosquitoes Direct infection* of man occurs through the introduction of the infected saliva of the mosquito into the victim's blood during the act of feeding *Accidental infection* may result from the use of a community syringe by drug addicts *Therapeutic malaria* is produced by the deliberate injection of the plasmodium in order to effect hyperpyrexia.

No race of man is immune to malaria but natives in endemic areas possess a relative immunity limited to the particular strain of parasite present in the environs This type of immunity is probably an acquired active immunity due to previous infection or to chronic malaria. Children are more susceptible than adults Climate is very important in the epidemiology of malaria since it limits the prevalence and habits of mosquitoes Soil, altitude and moisture are controlling factors in the breeding of mosquitoes and hence determine the prevalence of malaria in a given area In the northern part of the United States Anopheles mosquitoes exist but the season of optimal temperature for breeding is so short that malaria is unlikely to become widely prevalent

Immunity—*Acquired immunity* is common in malaria but the development of immunity to one strain of plasmodium does not protect against infection with other strains Active immunity to malaria is apparently dependent on the activity of the reticulo-endothelial cells which phagocyte the plasmodia Antitoxic and plasmodicidal substances apparently develop in the immune individual

Pathology.—Since malaria parasites destroy red cells a *hemolytic anemia* (p 1060) is a characteristic feature of the disease The rapid hemolysis of red cells results in the release of pigment which is deposited in all the viscera The most important pathological feature of the disease is the congestion and at times actual thrombosis of capillaries due to masses of plasmodia pigment red cells and mononuclear phagocytes This process is most intense in the spleen liver kidneys and brain

Coma, convulsions neurological signs and rapid death may be the result of capillary blockage in the brain *Splenomegaly* (p 1129) is a constant feature of malaria In acute stages the spleen is soft, but in chronic malaria it may become very firm and hard

Clinical Manifestations

Infection with all species of malarial parasites is characterized by the occurrence of *paroxysms of chills and fever* The interval between par

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6 7 Very tenuous medium trophozoite forms 8 Three ameboid trophozoites with fused cytoplasm 9 11 12 13 Older ameboid trophozoites in process of development. 10 Two ameboid trophozoites in one cell 14 Mature trophozoite 15 Mature trophozoite with chromatin apparently in process of division 16 17 18 19 Schizonts showing progressive steps in division (presegmenting schizonts) 20 Mature schizont 21 22 Developing gametocytes 23 Mature microgametocyte 24 Mature macrogametocyte

Courtesy National Institute of Health, U.S.P.H.S

The borders of the lesion are characteristically of a violaceous hue and are studded with pinpoint yellow miliary abscesses in which the organisms can be demonstrated Occasionally the lesions are punched out *ulcers* resembling gummas but are always surrounded by the dark colored borders containing miliary abscesses In this type of blastomycosis there are no signs of systemic reaction aside from pain due to the local lesions The health of the patient is unimpaired Untreated the lesions may persist for years but with proper treatment they tend to heal and the prognosis in general is good

The cutaneous manifestations of blastomycosis must be differentiated from tuberculosis verrucosa cutis lupus vulgaris and the nodular syphiloderm

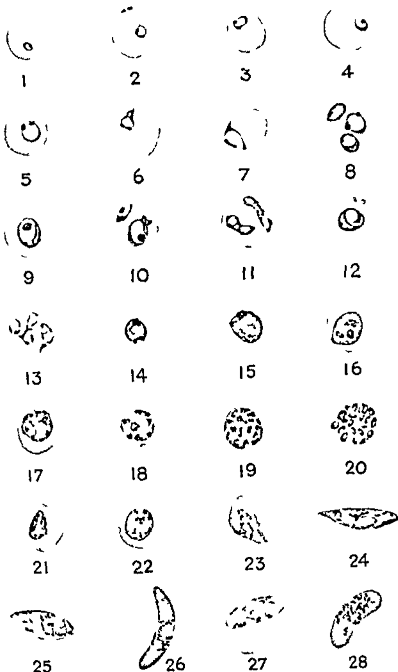


Fig 78—Blastomycosis of spine *

Tuberculosis verrucosa cutis is dry not crusted more indurated and lacks the minute abscesses in its borders It is most often observed on the dorsum of the hand *Lupus vulgaris* is most common on the face is dry contains the diagnostic apple jelly nodules and also lacks evidences of abscesses *Late syphiloderms* are usually dry never show abscesses and have typical odd gyrate or geometrical patterns the serology of the blood is positive and the lesions respond promptly to antisyphilitic treatment Ultimately the diagnosis of blastomycosis must be made by demonstration of the fungus by direct examination of pus by cultural or histopathological studies

Systemic Blastomycosis—In the systemic type of blastomycosis pulmo

* Conant, Martin, Smith Baker and Callaway Manual of Cli[illegible]



F 64—Pl mod m *falciparum.* 1 V y g g f m t pl t 2 D ble d t f cell tl g t t oz f m l f m, t e th t *form* 3 4 3 g troploz te b w g do bl brom tin dots 6 7 D l p g t pl t f m 8 Three med m troph z t cell 9 1 hoz t l g p g ue t cell co tai g M dots 10 11 Tw t ph l l of t cell h w g r tı f form which p ate m y as m 12 Alm f m t t pl z t h g l az f p m t thro gh t yt plasm M ure d t the cell 13 Est o t m l lender f ms. 14 M t t h t w g l ped t gm t 15 P as t th proc as f t l h mat d n 16 17 18 19 V ph ses f the d l pm t f th sch zont (preseg ment g sch zo te) 20 M t re schizo t. 21 22 23 24 S cc ss f ms the dev lopm t f th g m tocyte—ally not f d th pe pl l ulation 25 Imm t g m tocyt 26 M t m t cyt 27 Imm t e m cr g m tocyte 28 M t m cr g m tocyte

Co te y N t al I t t t l H alth U S P H S

countries in the world but appears to be most common in France. In the United States, up to a few years ago only a little more than 200 cases had been reported mostly from mid western states Most of the reported cases have been in manual laborers including farmers, gardeners and stablemen

Pathology—Sporotrichosis produces a granulomatous lesion which is not specific in nature The lesion consists of a necrotic center and a surrounding area containing epithelial cells multinucleated giant cells and a border of granulation tissue

Clinical Manifestations—Sporotrichosis is generally localized in the skin but may rarely involve the bones joints lungs or central nervous system Several clinical types of cutaneous involvement have been described In the European literature the lesions are reported as consisting of numerous small rubbery painless subcutaneous nodules which form cold abscesses The softening process only involves the center of the lesion resulting in a cup shaped depression surrounded by a firm and indurated zone At times there is a tendency to spontaneous ulceration of the lesions The regional lymph nodes are but rarely involved

In this country a somewhat different type of cutaneous lesions is more commonly seen The initial lesion or *chancre* is usually situated on an exposed part of the body especially on the fingers or the dorsum of the hand It frequently seems to follow trauma and may be an ulcer pustule gumma or abscess It may remain localized and solitary but more frequently the infectious process invades the regional lymphatics and produces a painless cordlike thickening of the lymphatic vessels This gives the appearance of subcutaneous gummas along the course of the infected lymphatics

The *cutaneous type of disease* is generally unaccompanied by constitutional symptoms The lesions develop slowly one by one often with a lapse of several months between the successive gummas Untreated the disease may last for years Death is usually the result of intercurrent infection or unrelated causes

Diagnosis—Sporotrichosis clinically may resemble *syphilis tuberculosis tularemia glanders* or *pyogenic infection* The ultimate diagnosis depends on culturing the organisms aspirated from unruptured abscesses It is rarely possible to detect the fungi in direct smears of pus Using killed cultures of sporotricha as antigens *agglutination* and *complement fixation tests* with the patient s serum and a skin test have been devised The accuracy of these tests is questionable and false positive reactions are apparently common

Treatment—The only drug which has proved of value in the treatment of this disease is *potassium iodide* The dosage is similar to that used for actinomycosis (p 492) Open lesions may be irrigated with Lugol s solution Abscesses may be aspirated but should not be incised as surgery is contraindicated in these cases *Roentgen ray treatment* may promote more rapid resolution of the lesion and *sulfonamides* and penicillin are worthy of trial Vaccine therapy may be attempted in patients who are refractory to iodides

TORULOSIS

Torulosis is a rare disease due to a species of yeast It is charactr by apparent selective localization in the central nervo, tem ar



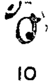



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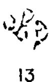



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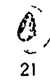



13 14 15 16






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21 22 23 24






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F 54 —*Pl mod m falcip* m 1 Y ry y g g f m t ph te 2 D bl nf t f gl cell, th y ung t phozo te m g k f m the tl gnet f m 3 4 Y g t pl tes h wi g d bl l m t dots 5 6 7 Dev l p g t phozo te f m 8 Th ee med m t ph t ll 9 T ph t h ng p m t, cell co ta g M d ts 10 11 Tw t ploz t h f tw cell h g t f f m h h paras te may as m 12 Alm t m t t ph t h w g h f p gm t th gl t cytoplasm M d t th ll 13 F t o- t mnal l d f m 14 M t t ph te l g l mped p gm t. 15 Paras te the p oc f t l h m t d n. 16 17 18 19 Y phas f the dev lop m t f tl sch t (p seg me t g sch ts) 20 M t sch zo t. 21 22 23 24 S ss f m the de l pment f the g m tocyte— ally t f d th pe ph l l t n. 25 Imm t m g metocyt 26 M t m m tocyte 2 Imm t re micr g m tocyte 28 M t re m g m tocyt

Co te y N t lI t t t f H lth U S P H S

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TORULOSIS

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oxysms depends on the duration of the schizogony cycle *P vivax completes its cycle in forty-eight hours The rupture of the infected red cells* and liberation of the merozoites correspond to the onset of the chill Since the cycle takes forty eight hours chills occur every third day (tertian malaria) *P malariae* has a cycle lasting seventy two hours and the chills recur every fourth day (quartan malaria) *P falciparum* has an irregular cycle and chills may occur every thirty six to forty eight hours

The regularity of the malarial cycle and the exact periodicity of the chills have been greatly overemphasized Mixed infections are not uncommon and even with a single strain of plasmodium there may be double or triple cycles so that the frequency of chills is quite irregular and the diagnosis of malaria can rarely be made by an inspection of the temperature chart

The *incubation period* for all three forms varies from ten to seventeen days

BENIGN TERTIAN MALARIA (P VIVAX)

In tertian malaria the *first chill* occurs ten to twelve days after infection For about five days before the first chill the patient is troubled greatly by *myalgia headache* and *malaise* which are often more incapacitating than the chills themselves During this prodromal period there is an *irregular fever* The chills begin suddenly but abdominal pain diarrhea nausea and vomiting may foreshadow their occurrence

The malarial chill lasts from five to thirty minutes during which time the temperature mounts rapidly to 105° or 106° F *Malaise myalgia headache nausea* and *palpitation* accompany the paroxysm and at times there is *confusion* or *delirium* After the chill there is almost complete symptomatic recovery As the temperature falls the patient experiences a *drenching sweat* falls asleep and awakens refreshed *Urticaria* is common after each chill and *herpes labialis* is generally present The *spleen* becomes palpable within ten days after infection and is especially large in tertian malaria Unless a new infection occurs it decreases in size over the course of a few months

The symptoms of the initial attack rarely persist longer than two months in untreated patients who are not reinfected Within two years malarial parasites can no longer be demonstrated in the peripheral blood Tertian malaria is fairly benign in young children although the spleen becomes very large In children under the age of 5 or 6 chills are not a feature of the disease

Except for rare instances of *ruptured spleen* complications are unusual in tertian malaria *Jaundice* is uncommon and the erythrocyte count is not often below 3 million per cubic millimeter in the uncomplicated disease Ankle edema is not seen in this form of malaria Coma and convulsions are very unusual

QUARTAN MALARIA (P MALARIAE)

Quartan malaria is characterized by a three day cycle but double and triple cycles are not unusual and produce a totally irregular temperature record The prodromal febrile period of tertian malaria is not found in the quartan type In quartan malaria there is less anemia than in any

Pathology —The acute disease is essentially benign and little is known of the pathology of this stage In the chronic disease the lesions produced are *infectious granulomas* resulting in fibrous tissue formation tubercles caseation and liquefaction necrosis with abscess formation and cavitation The cellular reaction consists of epithelioid cells lymphocytes plasma cells and giant cells of the Langerhans type The tubercles of this disease are quite similar to those of tuberculosis except for the presence of the double-walled refractile oval bodies of *coccidioides immitis*

CLINICAL MANIFESTATIONS

The clinical manifestations may be acute as in valley or desert fever They may be chronic and more sustained

Acute Coccidioidomycosis (Valley or Desert Fever)—The *acute disease* is characterized at onset by the symptoms of an upper respiratory infection and not infrequently by signs and radiographic evidences of bronchopneumonia *Erythema nodosum* develops one or two weeks after onset in



Fig 80 —Pulmonary coccidioidomycosis

from 2 to 5 per cent of the cases and persists for three to six weeks Other dermatoses are erythema multiforme and morbilliform rashes Cough blood streaked sputum chills fever sweats and backache occur simulating influenza or dengue fever Thoracic pain and cough are noted in 88 per cent and hemoptysis in 18 per cent

The *pulmonary lesions* as seen by roentgenographs show considerable variation in extent and character Hilar shadows and small solitary nodular areas of increased density may be areas of *confluent pneumonitis* particularly at the bases of the lungs In many instances the lesions appear predominantly exudative in character since they clear fairly rapidly Clearing may be incomplete however and is often followed by calcification (Fig 80)

* Courtesy of Dr C E Smith

organism is unknown and it is thought that an attack of blackwater fever may be precipitated by quinine It is closely associated with estivo-autumnal infections and occurs only in persons who have resided in endemic malaria areas

The attack begins suddenly with a chill and high fever The spleen enlarges rapidly and is tender but as hemolysis progresses it tends to shrink Within half an hour after the chill the urine becomes mahogany colored *due to the presence of free hemoglobin* The red blood cell count falls with amazing rapidity to a level of 1 million per cubic milli meter with a hemoglobin concentration as low as 10 per cent of normal *There is jaundice in every instance* and death commonly results from anuria or peripheral vascular collapse The case fatality rate is 20 to 30 per cent.

RELAPSES

Relapses occur in 90 per cent of untreated cases of malaria The cause of the relapse is probably the continued presence of parasites in the viscera When resistance is lowered the plasmodia proliferate again and clinical symptoms are again produced The first relapse usually develops from three to four weeks after the end of the initial attack

LATENCY AND CARRIERS

In endemic areas many adults have demonstrable parasites in the peripheral blood without symptoms These latent types of infection depend upon a balance between the host and the parasite which can easily be upset by an intercurrent disease fatigue or a surgical procedure Such persons are carriers and are of great importance in the transmission of the disease

DIAGNOSIS

The only certain method of diagnosis in malaria is the demonstration of *parasites in blood smears* stained with Wright s or some similar prepara tion Thick smears are preferable and the optimal time to take blood is toward the end of the febrile paroxysm In afebrile periods it may be dif ficult or impossible to find the parasites in the peripheral capillaries Various serological diagnostic tests have been proposed but so far none is of practical value Sternal punctures are of occasional diagnostic value False positive Wassermann reactions add confusion to the clinical problem See *Differential Diagnosis of Cryptogenic Fevers* (p 26) *Differential Diagnosis of Chills* (p 32)

PROGNOSIS

Death from *tertian* or *quartan malaria* is uncommon even if un treated Estivo autumnal *infections are always serious since fatal com plications* may develop with great suddenness The case fatality rate of estivo autumnal malaria is 20 to 30 per cent and 75 per cent of all malaria deaths are due to this form of the disease In any form of malaria pre-existing or concomitant disease makes the infection more serious

The extent of parasitization of troops engaged in the Pacific war theater makes it imperative for the astute practitioner to suspect malaria in any patient who has been recently returned from the Tropics The diagnosis is

oidin is of considerable help in differential diagnosis The test is performed by making an intracutaneous injection of 0 1 cc of 1 1000 and 1 100 dilutions This test is interpreted in the same sense as the tuberculin test If positive it means that the patient is or has been infected with coccidioidomycosis but his present illness may be entirely unrelated On the other hand if the test is negative it is unlikely that he is or has ever been infected by the organism It is not yet clear how soon after infection the skin reaction becomes positive but once positive it appears to persist indefinitely Blood precipitin and complement fixation tests are also available in expert hands

TREATMENT

No specific treatment for coccidioidomycosis is available The acute phase of the disease generally is self limited and requires only symptomatic treatment The chronic disease has been treated by a host of remedies including *colloidal copper iodides roentgen rays* the *sulfonamides* and *coccidioidal vaccines* There is as yet no clear evidence of the value of any

Trials with *promin* (p 98) and *penicillin* (p 106) have been suggested We should oppose the use of the former preparation but should advocate the latter together with streptomycin (p 114) since if nothing else is accomplished secondary invaders may be successfully eliminated

MONILIASIS

Monilia are ubiquitous inhabitants of plant life where they are probably saprophytic They are also occasionally cultured from normal skin mucous membranes and human feces It is likely that on human tissues they are either saprophytic or so feebly pathogenic that they are incapable of producing disease unless the tissues are devitalized by chronic disease or local trauma The finding of monilia in the feces of patients with tropical sprue led to the belief that they were responsible for that disease It is more probable that as a result of nutritional deficiency the intestinal secretions are altered and the resistance of the mucosa is lowered

Etiology—The skin and nails oral and vaginal mucosa intestinal tract and lungs may be infected by a number of species of monilia These are *yeastlike fungi* which reproduce principally by budding and appear in the lesions in the form of oval or round cells but which in artificial media form mycelia The different species in this large group vary in their ability to ferment sugars with or without the formation of gas and possess antigenic differences On Sabouraud s glucose agar they grow readily aerobically at room or incubator temperature The colonies are large and white or cream colored Microscopically round or oval cells are seen 3 to 10 μ in size These multiply by budding and in older cultures mycelia develop The fungus can be identified in human lesions by scraping the skin or mucous membrane lesions adding a few drops of sodium or potassium hydroxide (10 to 20 per cent) and examining under the microscope for the typical budding oval cells Sputum in cases of bronchopulmonary moniliasis may be examined in a similar manner (Fig 81)

CLINICAL MANIFESTATIONS

In the mucous membranes monilia infection (thrush) is common in young infants especially in foundling homes where oral hygiene is not too carefully maintained It is also sometimes seen in adults suffering from chronic debilitating diseases

Monilial vulvovaginitis (p 2598) is encountered particularly during pregnancy and in glycosuric diabetics Monilial cheilitis and occur

also against the erythrocytic asexual forms of the falciparum type In the test tube malarial parasites are still infective after twelve hours of incubation in a saline solution containing 1 10 000 quinine In the body quinine inhibits the multiplication of the plasmodia and causes most of the parasites to change into the sexual form In some ways there is a suggestion of a resemblance between the antimalarial action of quinine and the anti infective activities of sulfonamide and penicillin (p 88)

ANTISEPTIC ACTION —Quinine kills yeasts and bacteria in sufficient concentration (2 1000 to 8 1000) However molds grow freely in weaker solutions

LOCAL ACTION —Solutions of quinine salts are local irritants Gastric irritation leads to nausea and vomiting Hypodermic injections cause sterile abscess formation and extensive sloughs The occurrence of a large concentration of quinine in the urine produces renal damage with albuminuria and hemoglobinuria

ANESTHETIC ACTION —Quinine produces local anesthesia when it comes in contact with sensory nerves The compound used for this purpose is quinine and urea hydrochloride The anesthesia so induced usually lasts a *long time but is preceded by a preliminary stage of painful irritation* Local tissue necrosis resulting in sloughs may be produced The compound is freely soluble in water and is used in concentrations of 0.5 to 1 0 per cent

SCLEROSING ACTION —Quinine injected intravenously produces endophlebitis and venous thrombosis This action is utilized in the obliteration of varicose veins and hemorrhoids by the injection of solutions of quinine and urea hydrochloride (5 per cent) and quinine and urethane

MUSCLE ACTIONS —Quinine has a depressant action on *cardiac* and *skeletal muscle The action on the heart is similar to that of quinidine* (p 861) It prolongs the refractory period of cardiac muscle and decreases its excitability The rate of the heart is slowed and with moderate doses the amplitude of the cardiac contractions is increased The conduction of impulses by cardiac muscle is blocked and after large doses various degrees of atrioventricular block are produced The use of *quinidine* is superior to quinine in the treatment of *auricular fibrillation* and *ventricular tachycardia* It is important to keep the cardiac actions in mind since they are apt to cause side actions during antimalaria therapy

Quinine increases the refractory period of skeletal muscle and produces a direct curare like action The responses to a tetanizing stimulus and to acetylcholine are diminished or prevented The effects on skeletal muscle are the basis for the usefulness of the drug in *myotonia congenita* a condition characterized by the inability of voluntary muscle to relax after contraction (p 2886)

Moderate doses of quinine stimulate and large doses depress the contractions and tone of *uterine muscle* excised or in situ Stimulation increases with the duration of pregnancy The drug intensifies the periodic but weak labor pains but does not produce uterine spasm Toxic amounts of quinine may cause abortion

ANTIPYRETIC —Quinine lowers the elevated temperature like other antipyretic drugs by increasing heat loss The action is a direct one on the heat regulating centers of the hypothalamus Quinine also possesses anal

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In the mucous membranes monilia infection (thrush) is common in young infants especially in foundling homes where oral hygiene is not too carefully maintained It is also sometimes seen in adults suffering from chronic debilitating diseases

Monilial vulvovaginitis (p 2598) is encountered particularly during pregnancy and in glycosuric diabetics Monilial cheilitis and glossitis occur

gametocytes and schizonts of a quartan and tertian malaria as well as the sexual forms of malignant tertian malaria Unfortunately the original claims for plasmochin for the most part have not been sustained and the drug has but limited value as compared with quinine and quinacrine

In the usual therapeutic doses plasmochin is highly effectual against the sexual forms or gametocytes of falciparum malaria Its usefulness would appear to be limited to rendering non infectious the patient with falciparum malaria Its anti relapse activity in vivax malaria has been found to be disappointing

The drug is excreted at a slow rate in the urine and although appreciable quantities are destroyed in the body cumulative toxicity must be guarded against

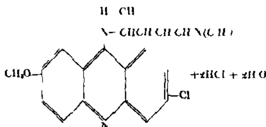
Toxicity—Plasmochin has an appreciable toxicity and should be used with extreme caution since the margin of safety is narrow Full doses produce *methemoglobinemia* attended by *cyanosis* Hemolysis is common and produces *jaundice hemoglobinuria* and *anemia* Toxic depression of the heart results from a direct myocardial depression and is marked by *tachycardia* and *cardiac arrhythmias* The use of the drug is frequently attended by nausea vomiting abdominal pain hepatic necrosis and in some cases acute yellow atrophy These considerations limit the use of plasmochin in patients with cardiovascular renal or liver disease Doses of 80 mg a day have caused death

Dosage and Administration—Plasmochin is dispensed in 10 mg (1/6 gr) doses and the maximum daily amount is 30 mg (1/2 gr) This drug should not be given for more than three consecutive days Each dose is given with 1 gm sodium bicarbonate a liberal carbohydrate diet and forced fluids It is given mainly to destroy the sexual forms which circulate in the blood These constitute a silent pool from which the mosquito may obtain organisms for the infection of new cases There is insufficient evidence that plasmochin reduces the relapse rate

Atabrine (Quinacrine U S P)—Atabrine was synthesized and introduced as an antimalarial in 1930

Chemistry—Atabrine is a substituted alkyl amino derivative of acridine with the following structural formula

QUINACRINE HYDROCHLORIDE.—Mepacrine Hydrochloride U.S.P.—Atabrine dihydrochloride—Contains not less than 77 per cent and not more than 80 per cent of quinacrine base $C_{23}H_{30}ClN_3O$ corresponding to not less than 98 per cent of $C_{23}H_{30}ClN_3O \cdot 2HCl \cdot 2H_2O$ U S P



It is supplied as the dihydrochloride a yellow powder with a bitter taste At room temperature it is soluble in water to the extent of 3 per cent When exposed to ultraviolet light a greenish fluorescence is observed

disease may be acute and bronchopneumonic or chronic resembling tuberculosis There is nothing distinctive about the radiographic or physical findings Bronchomycosis is particularly seen in tea tasters of Ceylon

The *diagnosis* can be made only by examination of smears and cultures of sputum It should be suspected in obscure chronic pulmonary disease in which tubercle bacilli cannot be found provided that monilia are repeatedly and consistently identified See *Differential Diagnosis of Commoner Febrile Intrathoracic Disorders* (p 404)

TREATMENT

The treatment of bronchial pulmonary and systemic moniliasis is unsatisfactory The iodides sulfonamides and penicillin are worthy of trial using massive dosages Injections of hyperimmune rabbit serum and vaccine therapy have also been suggested



Fig 82—Histoplasmosis of the knee

HISTOPLASMOSIS

In 1905 in the tissues of a patient dying of a disease resembling Kala azar Darling found enormous numbers of capsulated micro organisms in the reticulo endothelial cells of liver spleen lymph nodes and other organs The organism was regarded as protozoan and was named *Histoplasma capsulatum* In 1926 the first case was reported in the United States In 1934 De Monbreum succeeded in cultivating the organism and showed that it was a *yeastlike fungus* which exists in the tissues as round or oval bodies 1 0 to 4 0 μ in diameter chiefly within phagocytes In artificial cultures it forms mycelia Intravenous injection of suspensions of the organisms reproduces the clinical disease in monkeys The distribution of the fungus in nature and the portal of entry in man are unknown It is thought by some that the parasite gains entrance to the body through the respiratory tract while others favor gastro intestinal infection following ingestion (Fig 82)

* After Key and Large Journal of Bone and Joint Surgery 24

six days a week Another method is to give 0 05 gm (¾ grain) once daily after a meal and a dose of 0 1 gm (1½ grain) on the seventh day

In most instances the onset of clinical malaria is suppressed until after the drug is discontinued However in highly malarious regions it may fail to do this in some individuals After the drug is stopped it is usual for clinical malaria to appear in three or four weeks

Uses of Atabrine Other Than in Malaria—Atabrine is very effective in the treatment of *giardiasis* (p 1892) (intestinal infestation with *G lamblia*) Doses of 0 1 gm (1½ grains) orally three times daily after meals for two or three days produce a prompt disappearance of the cysts from the stools and in many cases relief of gastro intestinal symptoms

Chloroquine —Chloroquine (SN 7618) marketed as Aralen diphosphate *is a potent and relatively non toxic anti malarial whose formula is 7 chloro 4* (4-diethylamino-1 methyl butylamino) quinoline diphosphate It is prepared as a white powder and is available in tablets of 0 25 gm

Chloroquine possesses more than eight times the curative potency of quinine and it is 3 5 times as active as atabrine It is well absorbed and metabolized in the body only 10 to 20 per cent being excreted in the urine It does not cause significant untoward side effects nor color the skin Therapeutic doses at most produce transitory headache visual disturbances pruritus nausea or vomiting

Chloroquine is highly active against *P vivax* and *P falciparum* in their erythrocytic forms It does not prevent vivax relapses nor does it function as a prophylactic It does suppress vivax attacks and terminates acute bouts more effectively than atabrine For the treatment of an acute attack 1 0 gm (15 grains) *is given as the initial dose followed by 0.5 gm* (7½ grains) after 6 24 and 48 hours to total 2 5 gm (10 tablets) This regimen eradicates infection due to *P falciparum* and terminates the acute attack of *P vivax* Following *the latter suppressive therapy is required by the* administration of 0 5 gm (2 tablets) once daily at exactly seven day intervals

Paludrine —Paludrine (N1 para-chlorophenyl N5 propylbiguanide acetate) is an English product resembling chloroquine and of equal promise

Pentaquine —Pentaquine (NS 13 276) still another effective anti malarial is 6-methoxy 8 (5 isopropyl amino amylamino) quinoline It is employed as the diphosphate a yellow salt which is rapidly and completely absorbed and extensively degraded in the body Pentaquine is too toxic to warrant use in prophylaxis or prolonged suppression of malaria but may be used to cure *P vivax* invasions A daily dose of 80 mg of the diphosphate with 2 0 gm of quinine given concurrently in divided doses every four hours for 14 days produces radical cure of severe vivax infections

PREVENTION

The prevention of malaria is a public health problem of colossal magnitude as the disease is the greatest single cause of death and disability in many areas of the globe The essential feature of its control is the *eradication of the Anopheles mosquito*

In order to plan a campaign to eradicate mosquitoes in a given area

CHAPTER 25

PROTOZOAL INFECTIONS

Malaria (*Plasmodium falciparum vivax malariae* or *ovale*)
Amebiasis (*Endamoeba histolytica*)
Trypanosomiasis (*Trypanosoma cruzi gambiense* or *rhodesiense*)
Leishmaniasis (*Leishmania donovani infantum tropica* or *brasiliensis*)
Toxoplasmosis
Giardiasis (*Giardia lamblia*) (p 1892)
Trichomoniasis (*Trichomonas vaginalis*) (p 2598)
Balantidiasis (*Balantidium coli*) (p 1893)

MEDICAL protozoology is of increasing importance now that airplane travel has contracted the globe and military personnel have served in all parts of the civilized and uncivilized world

Comparatively few protozoa are demonstrably pathogenic for man Most live in a state of *commensalism* (p 37) The pathogenic protozoa may cause generalized or localized disturbances Systemic manifestations occur in *malaria amebiasis trypanosomiasis* and *systemic leishmaniasis* the digestive affections include *giardiasis* and *balantidiasis*, *Trichomonas vaginalis* is a local disturbance of the female reproductive system and *leishmaniasis* is a cutaneous infection

The United States Naval Medical School has prepared a useful classification of the protozoa of medical importance The following table has been adapted from it for present purposes The organisms whose names appear in capital letters are pathogenic for man and are described in the text those whose names are listed in normal type are commensals whose sole importance is their morphological similarity to the disease producing protozoa

Sporozoa (No organs of locomotion)
- PLASMODIUM
  - P FALCIPARUM
  - P MALARIAE
  - P VIVAX
  - P OVALE
    - See *Malaria* (p 507)
- *Isospora hominis*
- *Sarcocystitis lindemanni*

Endamoeba (Sarcodina move with pseudopods)
- E HISTOLYTICA
  - See *Amebiasis Endamebiasis Amebic Dysentery* (p 523)
- *E coli*
- *E gingivalis*
- *Endolimax nana*
- *Iodamoeba buetschlii*
- *Dientamoeba fragilis*

twenty four hours 1 gm (15 grains) of an alkaloidal salt is administered three times daily after meals Thereafter *for a period of seven days in vivax* malaria and ten days in quartan and falciparum malaria the patient is given 2 gm (30 grains) daily in divided doses In fulminating falciparum infections and those who cannot tolerate the drug by mouth a slow *infusion of 0 5 gm (7½ grains) is given intravenously* using 200 to 500 cc of physiologic saline as the diluent

For suppressive treatment 1 0 gm (15 grains) of quinidine is given daily for six days in the week *for three weeks following the last exposure to malaria*

Combined Treatment—Combined treatment using quinine and atabrine has been suggested by malariologists By this method quinine is given in doses of 0 65 gm (10 grains) *three times daily for the first three days in combination with 0 1 gm (1½ grains)* of atabrine At the end of the third day quinine is stopped but atabrine is continued until a total of 2.8 gm has been administered

For the *triple attack* on the infection the quinine-atabrine course is followed by a treatment holiday of two days Following this, plasmochin is given orally in doses of 0 01 gm. (⅙ grain) *three times daily after meals for three days*

Yet another combined attack has been suggested by the use of quinine and plasmochin Daily doses of 1.3 gm (20 grains) of quinine are administered together with 0.02 to 0.04 gm (⅓ to ⅔ grains) of plasmochin in three divided doses In malarial districts combinations known respectively as Plasmochin Compound and Chinoplasmin are widely used The former contains 0 12 gm of quinine and 0.01 gm of plasmochin the latter has 0 16 gm of quinine and 0.005 gm of plasmochin Either preparation is given three times daily for five days each *month in order to prevent relapses*

Blackwater Fever—When blackwater fever develops quinine and plasmochin are avoided and immediate efforts are made to restore blood volume by the intravenous drip of whole blood or a buffer solution In convalescence chloroquine or atabrine may be given very cautiously if the malarial fever persists but quinine and plasmochin are interdicted

AMEBIASIS (AMEBIC DYSENTERY)

Amebiasis is *an infection* with *Endamoeba histolytica* a protozoan organism Infection may result in an *asymptomatic carrier state acute* or *chronic dysentery* and may be followed by complications as abscess of the liver lung or brain Formerly regarded as primarily a tropical disease the Chicago outbreak of 1933 emphasized the *wide prevalence of amebiasis in America*

Etiology—*Endamoeba histolytica* exists as the motile *trophozoite* and the cyst The *trophozoite* varies from 18 to 25 μ in diameter It moves actively by means of pseudopodia, contains a nucleus numerous granules vacuoles and often ingested red blood cells The *cysts* are spherical bodies 5 to 20 μ in diameter surrounded by a refractile wall and containing *from 1 to 4 nuclei as well as rodlike chromatoidal bars* The morphology of the organism is best studied in preparations stained with hematoxylin or iodine (Fig 86)

Endamoebae histolyticae can be cultivated in the laboratory but after a number of transfers they tend to die out.

Pathogenesis—The natural habitat of the organism is the *lower bowel of man and other animals The cysts are the infective form since the trophozoite is destroyed by gastric juice*

The cysts are ingested and pass unharmed through the stomach and small bowel In the colon the organism emerges from the cyst wall and divides into a number of trophozoites which penetrate the intestinal mucosa and multiply in the submucosa producing the pathological and clinical features of the disease As organisms *again reach the lumen of the* bowel they become encysted and pass out in the feces

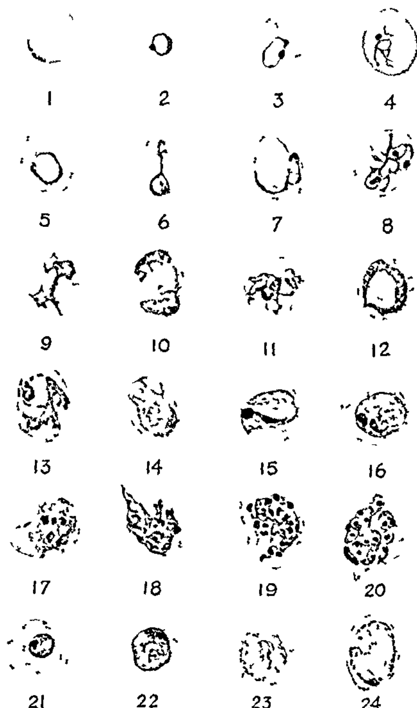


Fig 83—*Plasmodium vivax* 1 Normal sized red cell with marginal ring form trophozoite 2 Young signet ring form trophozoite in a macrocyte 3 Slightly older ring form trophozoite in red cell showing basophilic stippling 4 Polychromatophilic red cell containing young tertian parasite with pseudopodia 5 Ring form trophozoite showing pigment in cytoplasm in an enlarged cell containing Schuffner's stippling (Schuffner's stippling does not appear in all cells containing the growing and older forms of *P vivax* as would be indicated by these pictures but it can be found with any stage from the fairly young ring form onward)

maintain the motility of the trophozoites Repeated specimens should be studied before the examination can be considered negative Specimens may also be obtained through the sigmoidoscope

Cysts may be found in formed stools but never trophozoites If the stool is formed cysts are most easily found after a saline purge has been administered Oily medication must be avoided since the appearance of oil droplets is readily confused with that of amebic cysts

When the protozoa cannot be found by direct examination of the *fresh stool they sometimes may be demonstrated by preparing histological* sections of fluid stool or mucus after fixation and staining The characteristics of *E histolytica* are best summarized in the charts prepared by the United States Naval Medical School (Table 29)

Complement Fixation —A complement fixation test can be performed on the patient s serum and it is said to be highly specific The preparation of the antigen is rather difficult and the method is not widely used *Skin tests* are not yet available for routine diagnostic use



Fig 87—Amebae in stool Young and old trophozoites of *E histolytica* in stool

PROGNOSIS

The prognosis in acute cases of amebic dysentery which have been properly treated is good but in untreated patients the mortality may be as high as 30 or 40 per cent The more chronic the infection the poorer are the chances for complete restitution of the bowel Death seldom occurs during the initial attack of dysentery The prognosis in liver or lung abscess is favorable but the outcome in brain abscess is usually fatal

TREATMENT

AMEBACIDES

The treatment of amebiasis includes the management of acute amebic dysentery the chronic carrier state and the extra intestinal complications of amebic infestation such as liver lung and brain abscess For these conditions a number of drugs are available each of which has a certain specificity for the various phases of amebiasis

Mackie Hunter and Worth Manual of Tropical Medicine

TABLE 98 —DIFFERENTIAL CHARACTERISTICS OF THE THREE MALARIAL PARASITES (In *Stained* Thin Blood Smears)

	Plasmodium vivax	*Plasmodium malariae*	*Plasmodium falciparum*
Young trophozoite (Rings)	Signet ring forms size up to ⅓ diameter of red blood cell No pigment	Signet ring forms slightly smaller and denser than *P vivax* Cytoplasm deeper blue Fine grains of black pigment occasionally seen even at this stage Multiple infection of r b c very rare	Signet ring forms smallest of the species ⅕ diameter of red blood cell Cytoplasm thin hair like light blue Marginal forms common No pigment Multiple infection of r b c very common
Half grown and full grown trophozoite	Irregular sprawling outline with small and large masses and fine strands of cytoplasm Fine yellowish brown pigment	Cytoplasm compact in oval band ribbon & comet forms Black coarse granules or chunks of pigment The *most pigmented* species	Only ring forms grown up to ½ the diameter of the red blood cell and showing scanty dust fine black pigment evenly distributed Older trophozoites tend to disappear from the peripheral blood
Young and half grown schizont	Same as above except for division of chromatin in 2 or more masses	Same as above except for division of chromatin in 2 or more masses	Except for ring forms with 2 chromatin dots schizonts not seen in peripheral blood unless patient has very severe overwhelming infection
Full grown schizont	12 to 24 merozoites in irregular grape-like cluster Yellowish brown pigment massed eccentrically	6 to 12 merozoites arranged around a central mass of brownish black pigment the rosette or the daisy	Not seen in peripheral blood as noted above Best seen in spleen puncture smears 18 to 36 very small merozoites in irregular cluster Dark brown pigment massed eccentrically
Microgametocyte (Male)	Spherical or oval Cytoplasm stains pale blue Nucleus diffuse Pigment in short rods scattered irregularly	Similar to *P vivax* but smaller	Shorter and stouter than female more sausage shaped Cytoplasm pale blue Nucleus diffuse central Pigment scattered rather evenly through central ⅔ of parasite
Macrogametocyte (Female)	Spherical or oval Cytoplasm stains deep blue nucleus compact eccentric Pigment in long rods	Similar to *P vivax* but smaller	More pointed and longer than the male Nucleus more compact. Pigment clumped in coarser grains in the center
Character of the parasitized red blood cells	Larger paler than normal Eosinophilic stippling Schüffner s dots except in cells with the younger ring forms	Normal size and color No stippling	Normal size sometimes small r and distorted Brassy color Maurer s clefts or lots
The most outstanding features for differentiating the species	Parasites in various stages of development Sprawling light blue cytoplasm Parasitized cell enlarged pale with Schüffner s dots	Parasites in various stage of development schizonts common Compact, deep blue cytoplasm frequently oval or band shaped Pigment abundant Parasitized cell normal in size and color	Only rings or rings and crescents Ring small and delicate Multiple infections common Parasitized cells of normal size or smaller and distorted Numerous double dot schizonts an [illegible] que or accole

Emetine U S P *Pharmacology* —Emetine acts by destroying *Endamoeba histolytica* and affects the motile forms much more than the cysts

Therapeutic Use —Emetine is effective in vivo only on motile amebas It should be reserved for acute amebic dysentery and the exacerbations of chronic amebiasis Amebic hepatitis and abscesses in all extra intestinal sites also respond better to emetine than to any other antiparasiticide After emetine has effectively minimized extra alimentary infection an *other amebacide must be used to clear up the intestinal feeding focus* Mild amebic enteritis is best treated by chiniofon carbarsone or vioform

Toxicology —Being a general protoplasmic poison emetine damages the parenchymatous organs the heart and the voluntary muscles *Cardiac arrhythmias myocardial degeneration tremors weakness and pain in the muscles purpura* and *leukocytosis* may follow emetine *Gastro intestinal manifestations* including nausea vomiting diarrhea with marked debility are not uncommon sequels to its use The drug should not be employed in patients with cardiorenal disease or pregnant women It should be used most cautiously if at all for children Emetine is absorbed from parenteral sites Excretion in the urine and destruction in the body are very slow *making cumulation a definite possibility*

Methods of Administration and Dosage —Emetine Hydrochloride U.S.P may be obtained in 15 30 and 60 mg (¼ ½ and 1 grain) hypo dermic tablets to be dissolved for parenteral use Adults may take a maximum of 60 mg (1 grain) per day given if desired in two divided doses A course must not last beyond ten or twelve days For children over eight years 20 mg (⅓ grain) is the maximum No more than 10 mg (⅙ grain) per day can be risked for children below that age It is in general wiser to use other drugs if possible in children The preferred route of administration is by subcutaneous injection The drug should not be given intravenously Generally symptoms subside after several days of emetine *The drug is then stopped and chiniofon vioform or carbarsone is substi tuted* Emetine should not be repeated until six weeks have elapsed

Emetine is at times used in the form of emetine bismuth iodide a preparation suitable for oral administration A dose of 0 2 gm (3⅓ grains) in a hard gelatin capsule is taken after the evening meal daily for twelve days This drug though more potent than emetine alone compares un favorably with the more powerful amebicides chiniofon vioform and car barsone (Ipecac which contains emetine is now rarely used as an ameba cide because of the severe gastro intestinal irritation it produces)

Vioform N N R —*Vioform is a relatively nontoxic amebacide effective only in intestinal amebiasis* Unlike emetine it is more useful in chronic than acute amebic infestation though it acts on motile amebas as well as cysts It destroys the organisms on the mucosa and free in the intestinal contents Because of its low toxicity (iodism and gastric distress are the chief untoward manifestations) ease of administration and low cost vio form is suitable for mass treatment Vioform chiniofon and carbarsone given in alternate courses if necessary constitute the treatment of choice for carriers

Dosage and Preparation —The drug is given in 0 25 gm (4 grains) enteric coated or gelatin capsules Three tablets may be given three to four times a day for a ten-day course which may be repeated after a similar interval

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The most outstanding features for differentiating the species	Parasites in various stages of development. Sprawling light blue cytoplasm. Parasitized cell enlarged, pale, with Schüffner's dots	Parasites in various stages of development, schizonts common. Compact deep blue cytoplasm frequently oval or band shaped. Pigment abundant. Parasitized cell normal in size and color	Only rings or rings and crescents. Rings small and delicate. Multiple infections common. Parasitized cells of normal size or smaller and distorted. Numerous double dot schizonts and appliqué or accolé forms

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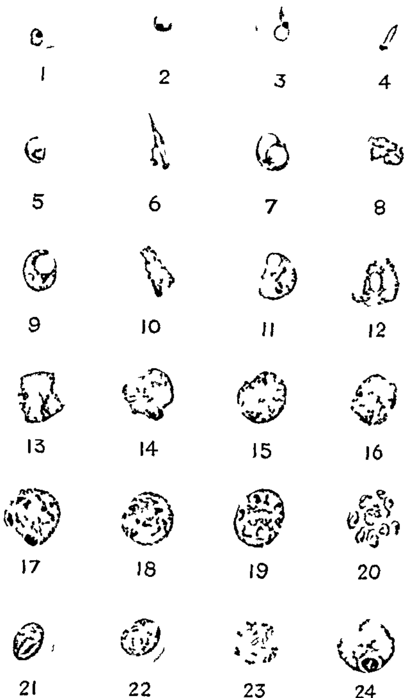


Fig 85—*Plasmodium malariae* 1 Young ring form trophozoite of quartan malaria 2 3 4 Young trophozoite forms of the parasite showing gradual increase of chromatin and cytoplasm 5 Developing ring form trophozoite showing pigment granule 6 Early band form trophozoite—elongated chromatin some pigment apparent 7 8 9 10 11 12 Some forms which the developing trophozoite of quartan may take 13 14 Mature trophozoites—one a band form 15 16 17 18 19 Phases in the development of the schizont ("presegmenting schizonts) 20 Mature schizont 21 Immature microgametocyte 22 Immature macrogametocyte 23 Mature microgametocyte 24 Mature macrogametocyte

Courtesy National Institute of Health U.S.P.H.S

of a week *vioform* is administered three times a day for seven days in 4 grain dosage by mouth At the end of this time a second treatment holiday is ordered and then the carbarsone is given for the final week If vioform is not available *chiniofon* (*yatren*) is substituted using 15 grains three times daily by mouth or *diodoquin* 0 6 grains

Carriers are given carbarsone in a dosage of 0 25 gm (4 grains) three times daily for seven days After a treatment holiday of a week vioform is then administered

For *amebic abscesses* particularly in the liver the emetine course is given for eight days There is a treatment holiday of three weeks and the course is repeated once or twice if necessary provided there is no toxicology Large abscesses that do not subside require surgical drainage Following the last course of emetine two or three courses of vioform are advised since carbarsone may not be as well tolerated by the already damaged liver

It is the opinion of the U S Navy that the rectal administration of carbarsone and chiniofon is futile

TRYPANOSOMIASIS

(*African Sleeping Sickness Chagas Disease*)

African sleeping sickness is caused by several species of *trypanosomes* The Gambian and Rhodesian forms of the disease occur in Africa and Chagas disease represents the South American variety

GAMBIAN TRYPANOSOMIASIS

Gambian trypanosomiasis is widely distributed throughout large areas of tropical Africa The causative parasite is a long spindle shaped *protozoan* 10 to 40 μ in length with an undulating membrane and a single flagellum It is transmitted to man by the bite of the *tsetse fly* (*Glossina palpalis*) A local inflammatory reaction is noted at the site of the bite This may persist for 48 to 72 hours The incubation period is 10 days to 3 weeks under usual conditions but may be as long as 5 years

The human disease is characterized by attacks of *irregular fever* with generalized *glandular enlargement* particularly of the posterior cervical chain The *nervous symptoms* include tremors mental disturbances apathy or somnolence and eventually coma and death Painful local edemas may be noted in hands feet and peri orbital regions and around various joints A deep hyperesthesia over the ulna is regarded as pathognomonic (Kerandel s sign) especially in association with enlargement of the posterior cervical glands (Winterbottom s sign)

RHODESIAN TRYPANOSOMIASIS

The *Rhodesian type* of sleeping sickness is limited geographically to a smaller area of Africa The *trypanosome* is morphologically similar to the Gambian variety The vector is another species of fly *Glossina morsitans* The human disease is similar to the Gambian type but the fatality rate is higher and it is more resistant to treatment

other type because there are so few parasites in the blood Splenomegaly is less prominent than in other forms of malaria

Quartan malaria is known for its chronicity and parasites may be detected in the blood more than ten years after infection There is considerable tendency to relapse but few serious complications appear except albuminuria edema and a tendency toward the development of nephritis

ESTIVO AUTUMNAL MALARIA (P FALCIPARUM)

Estivo autumnal malaria differs significantly from the other types in its symptomatology and prognosis Its severity is explained in part by its high invasiveness In quartan malaria there are a few hundred parasites in the circulating blood in the tertian variety there may be 10 000 parasites in the blood but in estivo autumnal infection they may exceed 500 000 per cu mm In estivo autumnal malaria schizogony occurs in the viscera and the parasites tend to cause agglutination of the erythrocytes resulting in mechanical blockage and *thrombosis in the capillaries*

Since there is no synchronization of the cycle *chills* can occur at any time The chills themselves are mild and last only a few minutes but the accompanying *malaise* and *myalgia* are more severe than in other types of malaria *Vomiting* and *epigastric pain* possibly due to perisplenitis are common during the chill Estivo autumnal malaria runs a short course and even in the untreated patient gametocytes are rarely found in the blood after several months

Falciparum malaria may present predominant nervous symptoms including stupor coma convulsions stiffness of the neck mental abnormalities and psychosis It may be preceded by initial coryza nausea vomiting and diarrhea so that it simulates a respiratory or an enteric infection It is only by recognition of the protean manifestations of malaria that the practitioner will avoid error in diagnosis

PERNICIOUS MALARIA

Estivo autumnal malaria may produce localizing signs and symptoms in any of the viscera and it is these severe and often fatal complications which give rise to the concept of a *pernicious malaria* In children estivo autumnal infection is particularly malignant *Anemia* may develop rapidly with a drop of 2 million red cells per cubic millimeter in less than a week *Cerebral symptoms* are extremely common and variable Hemiplegia convulsions coma aphasia optic neuritis and retinal hemorrhages may develop In the *cardiovascular system* anginal pain syncope and peripheral circulatory collapse may occur *Abdominal symptoms* may simulate appendicitis pancreatitis peritonitis cholera or gastro intestinal hemorrhage Severe *jaundice* with cholemia may result from toxic necrosis of the liver *Pneumonia* sometimes occurs in the course of pernicious malaria

BLACKWATER FEVER

Blackwater fever occurs most commonly in hyperendemic areas The predisposing factors seem to be numerous reinfections incomplete treatment chilling pregnancy or idiosyncrasy to quinine

Blackwater fever is an extremely serious condition due to an acute intravascular hemolysis Whether it is actually caused by the malarial

Acute Chagas disease is characterized by fever glandular enlargement and hepatosplenomegaly Trypanosomes are present in the peripheral blood whereas in the chronic stages they occur only in the viscera

Thus far there has been no satisfactory treatment developed for Chagas disease in contradistinction to the therapeutic results later discussed that give promise in other varieties of trypanosomiasis

Diagnosis

In both forms of the African trypanosomiasis diagnosis depends on the identification of the parasite in the *blood* or tissues Wet blood smears may contain the organism which can be seen thrashing about among the red cells *The organisms are not plentiful in the peripheral blood and may* be difficult to demonstrate Under such circumstances *aspiration of fluid from lymph nodes* may yield the trypanosome which is also sometimes present in the *spinal fluid* once nervous symptoms have made their appearance Direct microscopy may be supplemented by injection of material into rats guinea pigs or monkeys and observations of the experimental animal

Treatment

In the treatment of trypanosomiasis a number of drugs have been employed including *arsenicals antimony* and a group of complicated *synthetics* The most useful arsenical is *tryparsamide* (p 120) which has superseded the older remedies such as *atoxyl* (*sodium arsenilate*) and the various *antimony* preparations The second choice of those who have studied these diseases most closely are the synthetics such as *germanin* (Bayer) *moranyl* (Fourneau) *antrypol* and *naphuride* (Winthrop) These are similar in composition and are symmetrical ureas of sodium *m* amido benzoyl *m*-amino *p* methylbenzoyl *l* naphthylamino 4 6 8 trisulfate

The United States Navy suggests the following plan of treatment in the *early cases of the Gambian type* A course of 15 weekly intravenous injections of *tryparsamide* is given The initial adult dose is 1 to 1.5 gm (15 to 22 grains) dissolved in 10 cc of distilled water avoiding the use of saline solution If there are no toxicological phenomena the individual dose is increased to 2 gm (30 grains) and then 3 gm (45 grains) As an alternate *naphuride* (*Winthrop*) or *germanin* (*Bayer*) is injected at four day *intervals for four to six doses The initial adult dose is 0 3 to 0 5 gm (5 to* 7½ grains) given intravenously in 10 cc distilled water If there are no *toxic phenomena the individual dose is increased to 1 gm (15 grains)* In early cases of the *Rhodesian type* tryparsamide is ineffective and treatment is immediately started with *naphuride*

In the *late cases* of either the Gambian or the Rhodesian variety tryparsamide is the only drug of value and a course of 20 weekly injections is advised with a repetition after an interval of one to three months

An innovation of great promise in the treatment especially of *T gambiense* is *p-arsenophenylbutyric acid* Twelve to fourteen daily injections of 0.5 mg per kg or six to seven daily injections of 1 0 mg per kg effect definitive cures in early infections The drug has negligible toxicity and may eventually prove the most effective trypanocide

eliminated only if repeated thick and thin blood smears are examined at intervals of twelve to twenty four hours for several days Even then under suspicious circumstances a therapeutic trial with the anti malarial drugs is advised

The technic of making the thick blood smear is worthy of attention The specimen is preferably collected twelve to twenty four hours afte the chill and slides are used which are clear unscratched and meticulously clean They must be free from grease dust acids and alkali The skin is well cleansed before the prick is made and the alcohol is permitted to dry so that it does not mix with the blood A good stab is made so that the blood wells up in a large drop without excessive pressure An area the size of a dime at the end of the slide is then covered with as much blood as can easily spread without cracking or peeling after drying It hould be so thick that ordinary printing can be just read through the wet center of the film The slide is then put aside to dry and stained immediately The other end of the slide may be prepared with the usual thin film which may be of some assistance in confirming the identification of the species

ANTIMALARIAL AGENTS

The anti malarial agents include quinine totaquine plasmochin ata brine chloroquine (SN 7618) paludrine and pentaquine (SN 13 276)

Quinine—Quinine an alkaloid derived from the bark of the cinchona tree is one of the most commonly employed drugs in the world today This is due to the wide prevalence of malaria which ranks first among the diseases afflicting the human race At one time quinine was also employed as an antipyretic in nonmalarial fevers but has been replaced in this sphere by more effective synthetic drugs (see *Analgesic Antipyretics* p 3532) Certain derivatives of quinine the hydrocupreines have been exten sively studied as chemotherapeutic agents Because of their toxicity these compounds have found an extremely limited clinical acceptance

Source—Quinine is one of a group of more than twenty related al kaloids found in the various species of the two rubiaceous genera Cin chona and Rimijia plants originally found on the eastern slopes of the Andes usually from 5000 to 8000 feet above sea level After its intro duction into Europe by the Jesuits in the seventeenth century the demand for Jesuits (cinchona) bark became so great that attempts were made to cultivate the trees in Jamaica Australia India Ceylon and Java Today Java is the richest cinchona district in the world

The cinchona alkaloids are contained in the parenchymal cells of all parts of the plant The bark especially that of the root is richest in alkaloids yielding 18.5 per cent quinine Although more than 600 tons of quinine are produced each year this is not sufficient for the true needs of the malaria infected population of the world

General Pharmacology and Therapeutics—In sufficient concentration *quinine* is toxic to all cells leading to depression and death It concentrates at the cell surfaces and hinders catalytic phenomena by interfering with normal surface condensations This action tends to diminish the permeabil ity of the cell and arrests cell movements

ANTIMALARIAL ACTION—Quinine is highly effective against the erythro cytic asexual and the sexual forms of both vivax and quarta malaria and

neostam (stibamine glucoside) *solustibosan* (Bayer) and *neostibosan* (Bayer) The last named is least toxic and its use is recommended by intravenous injection A course of 15 doses is given on alternate days The initial amount is 0 2 gm (3 grains) and subsequent doses are 0 3 gm (5 grains) Ampoules contain 0 3 gm (p 133)

A freshly prepared 2 per cent solution of *potassium antimony tartrate* (*U.S.P.*) is also used in the treatment of kala azar An initial dose of 2 cc (0 04 gm) is injected intravenously A course of 40 or more injections is given unless toxic symptoms develop After noting the response to the initial dose succeeding doses are increased by amounts of 1 cc until the maximum single dose of 5 cc has been reached (0 1 gm)

In the Egyptian Sudan where the disease is resistant to antimony the United States Navy recommends the use of *stilbamidine isethionate* (4 4 diamidino stilbene isethionate) by intravenous injection A freshly

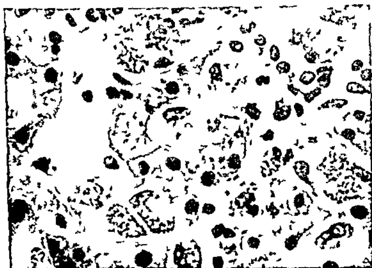


Fig 89—Liver in kala azar with Leishmania donovani in the phagocytic Kupffer cells *

prepared solution is made up in 10 cc of sterile distilled water which must not be heated The initial dose is 1 0 mg per kilogram of body weight and the maximum dose is 0 15 gm given every other day for 15 injections If patients show a tendency to a fall in blood pressure syncope or fainting after the early injection they should be protected by the injection of a small dose of epinephrine During the course of treatment the liver is protected from damage by the administration of calcium and dextrose

TOXOPLASMOSIS

Toxoplasmas are minute protoplasmic masses that are distinctly oval pyriform rounded crescentic or elongated Each has a more or less central nucleus and is capable of parasitizing vertebrate hosts Organisms occur singly or in clusters in the host cell and multiply by repeated binary fission Toxoplasmosis is endemic in rodents and domestic animals It may cause

* MacCallum, Textbook of Pathology

gesic properties useful against headache and neuralgias

STOMACHIC AND TONIC—The extremely bitter quinine salts and cinchona preparations are used to stimulate gastric tone and appetite If the dose is too large gastric secretion is inhibited and nausea and vomiting may result from the local irritative action on the gastric mucosa

Therapeutic doses of quinine (1 to 2 gm [15 to 30 grains] daily) lead to *cinchonism* characterized by headache ringing in the ears and disturbed vision Larger doses may cause photophobia deafness and blindness These are due to quinine susceptibility of the nervous elements of the retina and the inner ear

Quinine amblyopia usually occurs after moderate doses in susceptible individuals This condition is characterized by a widely dilated pupil, contracted visual fields and blindness The retinal vessels are in spasm the disk appears pale and anemic Anemia of the fundus causes degeneration of the retinal ganglion cells and nerve fibers and eventually causes optic atrophy The same reactions are seen with *optochin* (ethylhydrocupreine) formerly used in the treatment of pneumonia and pneumococcal conjunctivitis

Large doses lead to a fatal depression of the central nervous system marked by convulsions unconsciousness and death from respiratory paralysis The fatal dose of quinine varies from 8 to 30 gm Intravenous injection may be attended by collapse Hematuria albuminuria and hemoglobinuria are signs of renal damage

Fate of Quinine in Body—Quinine when given orally, is rapidly absorbed from the small intestine Rectal absorption is poor and the rectal route is irritating The absorbed drug is quickly removed from the blood Sixty per cent of the total amount is destroyed in the liver 40 per cent is excreted unchanged in the urine The excretion of the drug is impaired by renal damage It is important to recognize that quinine toxicity is increased by *renal* and *hepatic* damage

Treatment of Quinine Poisoning—If recently ingested the drug may be removed from the gastro intestinal tract by *gastric lavage* and *saline cathartics* after *alloidal precipitating agents* (e g strong tea 1 per cent potassium permanganate solution) have been given Appropriate measures for the elevation of blood pressure may be needed This has the double function of improving the general condition and increasing renal blood flow to speed the rate of elimination of the drug Caffeine ephedrine and epinephrine are used for stimulation Epinephrine is used to combat allergic manifestations To maintain proper oxygen exchange carbon dioxide and oxygen inhalations as well as artificial respiration are sometimes necessary Residual visual disturbances may respond to vasodilator drugs

Totaquine—Totaquine which contains a small percentage of quinine supplemented by quinidine cinchonine and cinchonidine is practically as effective as quinine for oral medication It has been adopted by the United States Pharmacopoeia Totaquine may be substituted for quinine effectively in doses of 0 6 gm three times a day for seven days Some relapse cases may require the continuation of treatment at one half of this dosage for two to three weeks

Plasmochin (Pamaquine Naphtholate)—Plasmochin is a derivative of methylene blue It was introduced in 1926 as an effective agent against the

CHAPTER 26

HELMINTHIC INFECTIONS

MEDICAL helminthology like protozoology is no longer a problem of tropical countries Helminthic disease is worldwide in distribution The infecting organisms include *nematodes (round worms) cestodes (tapeworms)* and *platyhelminthes* (flatworms) The last of these are systemically the most invasive They include *flukes* that involve blood stream bladder liver intestines and lungs *Tapeworms* with the exception of Echinococcus granulosus productive of hydatid cysts are essentially inhabitants of the gut *Roundworms* rarely travel beyond the intestinal mucous membrane except in certain cases of hookworm disease trichinosis and the *filarial disturbances*

Practical considerations make it advisable to present the material on helminthiasis with reference to the affected tissue rather than the nature of the invading organism In consequence the reader is referred to the Sections listed below for more complete details

Systemic Helminthiasis (see below)
- Hemic Distomiasis (Schistosomiasis Bilharziasis Oriental or Vesical Blood Flukes)
- Trichinosis

Intestinal Helminthiasis (p 1893)
- Distomiasis (Giant Intestinal Flukes)
- Teniasis (Tapeworm)
- Echinococcosis (Hydatid Disease)
- Oxyuriasis (Pinworm Seatworm)
- Uncinariasis (Hookworm)
- Strongyloidiasis (Cochin China Diarrhea)
- Ascariasis
- Trichiriasis (Whipworm)

Pulmonary Helminthiasis (p 2213)
- Pulmonary Distomiasis (Oriental Lung Fluke)

Hepatic Helminthiasis (p 1989)
- *Clonorchis sinensis* (Chinese Liver Fluke)

Filariasis (p 3321)
- *Wuchereria bancrofti* (Filariasis)
- Loa loa (Eyeworm)
- *Onchocerca volvulus* (Blinding Filaria)
- Mansonella
- Acanthocheilonema
- *Dracunculus medinensis* (Dragon Guinea or Medina Worm)

HEMIC DISTOMIASIS

(*Schistosomiasis Bilharziasis*)

The pathogenic helminths include a variety of flat worms (Trematodes) some of which produce systemic infection Most important of these are the

in aqueous solutions up to 1 part in 5 million This is the basis of a method used for determination of the atabrine concentration of the blood by means of a *photoflorometer*

Pharmacology—Quinacrine like quinine is highly effective against erythrocytic asexual and sexual forms of vivax and quartan malaria and against erythrocytic asexual forms of falciparum Quinacrine is almost two hundred times more active than quinine and has a greater margin of safety

Like quinine, atabrine is rapidly absorbed from the small intestine The plasma concentration of the latter rises more slowly however since the drug is first taken up to a large extent by the tissues On the other hand the excretion of atabrine is slow and occurs chiefly by way of the urine Significant fecal excretion of atabrine does not occur Cumulative toxicity is produced with ease Atabrine being a yellow dye stains the tissues and urine yellow in about 50 per cent of individuals to whom it is given The discoloration may persist for two or three weeks after the drug is stopped it must not be mistaken for jaundice

Toxicity—Although atabrine is safer than plasmochin it possesses some toxicity in therapeutic doses Nausea vomiting and diarrhea are frequently encountered headache dermatoses psychoses hepatic damage may be observed in some patients When these symptoms occur they usually follow the first few doses and are more apt to be present if the remedy is given between meals In most cases these symptoms may be prevented by giving sodium bicarbonate and sweetened drinks with the drug

There is some evidence that therapeutic doses of atabrine may cause occasional hepatic damage

Doses and Administration—To obtain an effective concentration of atabrine in the plasma as rapidly as possible large doses are used by mouth and are followed by smaller maintenance doses In uncomplicated malaria the drug is given in doses of 0 2 gm (3 grains) every four hours for 5 doses These are followed by 0 1 gm (1½ grain) three times daily after meals for six days One gram of sodium bicarbonate should be given with each dose and fluids should be forced

In patients who are comatose or vomiting or with persistent parasitemia despite adequate oral doses the drug should be given parenterally Two tenths of a gram of atabrine dihydrochloride in 7 cc of sterile normal saline should be injected into the muscles of each buttock A subsequent injection of 0 2 gm should be repeated every eight hours until oral medication is possible

Unlike quinine there is no evidence that atabrine ever induces black water fever In fact it is claimed that the use of atabrine has sharply reduced the occurrence of this complication In the treatment of acute attacks of hemoglobinuria in malaria patients however it seems best to avoid atabrine until the blood destruction has ceased and to depend on alkalies and blood transfusions Atabrine like quinine may be used during convalescence

Malaria Suppression—Atabrine is generally regarded as *most effective* in malaria prophylaxis Experience in World War II indicates that it is better tolerated than quinine The recommended dosage is 0 1 gm (1½ grains) of atabrine dihydrochloride once daily at the evening meal for

compound Daily doses are given for the first three days The initial amount is 1.5 cc (22 minims) If there are no untoward symptoms the second dose is 3 5 cc (52 minims) and the third injection is the full 5 cc (75 minims) amount Thereafter on alternate days until a total of 10 doses has been injected 5 cc are given intramuscularly At the completion of the first course of treatment a repetition of the course is warranted if eggs contain ing living embryos are still demonstrable The toxic symptoms of fuadin administration include vomiting and joint pains (p 133)

If three courses of fuadin fail to produce a satisfactory response a freshly prepared 0 5 per cent solution of *potassium antimony tartrate* is in jected intravenously with the greatest care The initial dose is 10 cc Injec tions are made on alternate days increasing the total amount by 5 cc until the full dose of 30 cc can be given A complete course consists of 12 to 15 injections

The toxicity of the tartrate solution requires that the injection be made at least two or three hours after a light meal The patient is ordered to lie down for an hour after his injection Infiltration of the vein will lead to serious thrombosis rapid introduction produces grave immediate symp toms including coughing nausea vomiting dizziness and collapse While the patient is receiving the drug the diet is to be high in carbohydrate and low in protein Supplementary feedings of vitamin A and B complex are advisable The treatment may be repeated after a month

Prevention—Schistosomiasis is prevented by immediate and complete scrubbing of the point of entry using soap and pure water In artificial pools a 1 2000 solution of copper sulfate will kill cercariae and snails

TRICHINOSIS

Trichinella spiralis is a *round worm* that is worldwide in distribution Its principal reservoir for human infection is the *pig* Man becomes afflicted as the result of eating incompletely cooked pork In the United States the incidence of infection as determined by postmortem examination of dia phragms is estimated at 17 per cent by the United States Public Health Service

The *T spiralis* occurs most frequently in *pigs man* and *rats* It is occa sionally found in dogs bears foxes and other carnivora All hosts harbor both the adult and the larval stages

Man becomes infected by eating raw and insufficiently cooked meat which contains *encysted larvae* After ingestion the cyst capsule is digested and the larvae are set free They attach themselves to the walls of the duodenum and jejunum In these localities they grow to the adult stage within a few days The male form which is approximately 1 5 mm in length impregnates the female which is 3 mm in length and then dies

The *fertilized females* penetrate the mucosa and within twenty four hours begin to deposit larvae These *measuring only 0 1 mm* in length are carried by way of the *portal blood stream* to the *systemic circulation* and are distributed to the various organs Only those which reach *striated muscle* survive and the sites of predilection include the *diaphragm tongue pectorals* and *intercostals*

In the striated muscle the larvae penetrate the individual muscle fibers and grow to a length of 1 mm They then coil up and become *encysted* remaining viable in this state for twenty years or more

factors which must be known include the breeding places and their distance from human habitation the usual radius of flight the numbers of each variety of mosquito their seasonal prevalence their biting habits and their tendency to enter human habitations Altogether there are over 180 species of the Anopheles mosquito but the majority of them are not of importance because their biting habits do not bring them into close and repeated contact with man It has been said that the successful malariologist must learn to think like a mosquito Any discussion of the technics of mosquito control is beyond the scope of this volume

Individual prophylaxis consists in avoiding mosquito bites This is obviously a difficult and generally an impossible task Visitors to endemic malaria areas should sleep beneath mosquito netting and use mosquito repellent lotions of which there are several highly effective preparations (p 3118) Most efficient mosquito control may be anticipated from DDT perfected by military agencies of the United States

Treatment —Effective treatment of malaria consists in administration of chloroquine (aralen) atabrine or quinine reserving plasmochin for the single indication of rendering the patient with falciparum malaria non infectious to mosquitoes

Chloroquine (Aralen) Treatment—At present writing (Feb 1947) Aralen diphosphate or Chloroquine (SN 7618) appears to be the most efficient and safest anti malarial Dispensed in tablets of 0 25 gm a dose of four tablets (1 0 gm) is given for the treatment of an acute attack Three additional doses each of two tablets (0.5 gm) are given respectively after 6 24 and 48 hours to total 2.5 gm For suppression 2 tablets (0.5 gm) are given once daily at seven day intervals

Atabrine (Quinacrine) —The use of atabrine produces effective anti malarial effects In the conscious patient 0 2 gm (3 grains) is given at the time diagnosis is established Thereafter at four hour intervals doses of 0 2 gm are repeated until a total of 1 0 gm has been given The dose is then reduced to 0 1 gm (1½ grains) three times daily for six days until a total of 2 8 gm has been administered

The patient with *falciparum malaria* and those who are unable to swallow the drug are given intramuscular injections of 0 2 gm (3 grains) into each buttock using 10 cc of sterile distilled water as a diluent If it is necessary to continue injections 0 2 gm (3 grains) are given at eight hour intervals until a total of 1 0 gm (15 grains) has been administered Then the intervals are increased to twelve hours until oral doses can be instituted using 0 1 gm (1½ grains) three times daily until a total of oral and parenteral amounts reaches 2 8 gm

Following atabrine therapy the patient rarely has more than one paroxysm Those with *vivax malaria* usually have a recurrence within one to twelve months unless suppressive treatment is instituted The latter may be accomplished by giving 0 1 gm (1½ grains) after a meal once daily for six days in the week over a three week period following the last exposure to malaria *Atabrine and plasmochin* are not to be given simultaneously under any circumstances Quinine may be given with either of the other antimalarial agents

Quinine—Quinine may be utilized for the same purposes as quinacrine though the older preparation is less effectual than atabrine During the first

The cycle of infection is completed when the muscle food is ingested and the larvae are again freed It is said that a single female gives birth to more than 1000 larvae which are demonstrable not only in the skeletal muscle but also in the heart the cerebrospinal fluid the bone marrow and the milk of nursing mothers

Clinical Manifestations—In the vast majority of instances infestation with the *T spiralis* produces no recognizable symptomatology Certainly of the 17 per cent of Americans whose diaphragms at autopsy reveal the organism only an infinitesimal number can have developed symptoms since clinical trichinosis is rarely observed in private or institutional practice

In its classical form trichinosis produces a *generalized febrile reaction* which may be transitory or protracted We observed one patient who had temperature for more than 100 days The onset of the disease is often associated with *abdominal distress* and a *mild diarrhea* corresponding to the

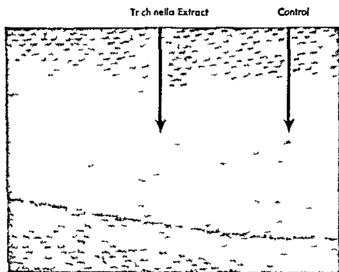


Fig 91 —Positive intracutaneous test for trichinosis

period when the larvae inhabit the upper bowel With systemic dissemination of the organisms the patient develops a triad of suggestive symptoms (1) the stained *blood* reveals an *eosinophilia* (2) localized *muscle pains* and *tenderness* are noted in the regions of the biceps triceps and gastrocnemii and (3) an *edema* is seen beneath the eyes or involving the entire face

See *Laboratory Aids in Diagnosis of Infectious Fevers* p 30

The course of trichinosis is variable The majority of patients recover so rapidly that the diagnosis is apparently never established In the rare and severe manifestations the febrile period continues and the patient becomes progressively more toxic and exhausted If *cerebral symptoms* develop the organism may be demonstrated in the cerebrospinal fluid *Cardiac infestation* occurs with demonstrable abnormalities in the electrocardiogram Death may result from progressive toxemia or pulmonary manifestations

Courtesy of Eli Lilly and Co

may produce a visible bulging between the lower anterior ribs on the right side See *Differential Diagnosis of Commoner Febrile Intrathoracic Disorders* (p 404)

The unrecognized and untreated liver abscess may rupture into the peritoneum and produce a *peritonitis* which is generally fatal More often it evacuates under the diaphragm and subsequently ruptures producing an *empyema* or a *lung abscess* which may later drain through a bronchus when the pus is coughed up in the sputum

Diagnosis—Amebic liver abscess can be diagnosed with certainty only by *aspirating the pus* and finding *amebae* The pus is viscid chocolate-brown (*anchovy sauce*) and contains few leukocytes unless there is bacterial infection Whenever pus is obtained from a liver abscess lung abscess or empyema amebic infection should be considered



Fig 86—Subacute amebic abscess of the liver with amebae in crevices of loose connective tissue *

BRAIN ABSCESS

Brain abscess is a rare complication of liver abscess or of lung abscess the infection travelling by way of the blood stream The symptoms are similar to those of other types of brain abscess and the prognosis is equally poor

DIAGNOSIS

Stool Examination—The definitive diagnosis of amebiasis requires the *identification of the amebae in feces* an examination which demands considerable technical skill since other amebae such as the nonpathogenic *Endamoeba coli* must be differentiated The stool is examined immediately after it is passed and should be kept warm under the microscope in order to

* MacCallum. Textbook of Pathology

the offending larvae have already invaded the musculature by the time the diagnosis is suspected

Prevention —Trichinosis is effectually prevented by eating no pork at all or else only pork that has been cooked at a temperature of over 150° F for more than an hour or more properly at 35 minutes per pound Pork frankfurters are especially dangerous since these meats are often either undercooked or raw Cured ham is usually safe if it has been purchased from a large manufacturer but smoking by one who is not licensed may have considerable risk Bacon is safe since the cysts are not found in fat but lodge particularly in muscle fibers

TABLE 29 —DIFFERENTIAL CHARACTERISTICS OF THE INTESTINAL AMEBAE
(Normal saline smear)

	E h stolytica	*E col*	*E nana*	*I butschl*	*D f agus*
LIVING TROPHOZOITES					
S ze (i mi- c on)	6 to 40 m ll race a. 8. Large rac I carr rs ca. 14 1 dysentery ca 4	12 t 30 Usually abo t 0	6 to 12 U ually about 8	6 to 20 Usually bout 10.	6 to 18 U ually abo t 1
Sl pe whe at est	Rounded but sl gl tly irreg lar	Same.	Same.	Same.	Fa ltlessly spherica (distinctiv).
M t l ty	Pseudopod a tongue-l k protrud d w th e plo e for Sometimes in e d re tio a d in r p d ceas g i g ise to p gres- sive di ect o l crawl (*For d era i d agnostic*) In ld forms pseu d pod m lar to *E ol* and *E n na*	Pse dopodi broad [cr scent haped] somet mes budd g, luggishly protruded nd las ly with- d wn. Rar ly in al gnish progress v directional crawl.	Pseud pod a small, b dd ng, knob-l ke, overlapp ng. Little or no progression	Same as *E coli* ne e in progressi e di- rectional crawl.	Th n, eil-l ke, fan-shaped, trang lar or recta g lar or leaf-like with f rp corners or ro la (diagnostic) N pro- gression.
Endo- plasm d ts i l ns	End plasm l R B C's gest d i the p esence f blood as e g. n amoeb c dyse tery (diagnosti)	E d plasm d rty due to i act ria nd food d bris. Ingested R.B C's seen ery arely	Same as *E ol* N i gesti f R.B C's.	Same as *E l* No gest on of R.B C'	Cytoplasm th n, in-gested bacteri and food show eal No ngestion of R.B.C s.
Vis l l ty f cle	I isible e pt fi w ng d plasm d ri g progressi c i wh t m y be see as a dimly tl ed ri g In ld t oj hoz tes d g ted n cleus le ly is ble as tl k i	Almost alw ys visible as a greyish or black g en in fresh tr ph tes.	Somet mes seen as a greyish-blue disc. (Not l ar no gh t be of diagnostic importance.)	Same as *E nana.*	Not visibl
LIVING CYSTS					
S (i mi- c ons)	5 t 16 Sm ll bo t 8 La ge rac b t 12	10 to 30 A era 17	6 to 10 U ually 8.	6 to 16 Usually 10	N ysts.
Sh pe	R nd d b t ld m perf ctly spherical	Sam	Ro ded, ov l sausage-shaped (di ag ost)	R unded or odd sh ped triangular pear r k di y sh ped (diagnosti)	N c ts.
Chro- m toid matter	Ab dant B rs with rou ded end or g sh p d od (d agi ostic) Pres- t n f 0 to 100 us ll in mo e th 50% of th cy ts.	Sc ty Sp cules or blocks w th sharp po nts (d g ostic) Seld m seen in th 10% f th cysts.	No e.	N e.	N c ts.
Gly cogen.	R ly fi nt amount to hange ppear of y t.	You g cy ts filled w th gly g h e m ddy cytoplasm.	No glycog n isible.	Major ty h w ll de-fined d nse glycog f ll, l gh ly refrac-tile, l ght-bl e (di agnostic)	N ysts.
V l t n gra les.	N e.	N e	N e	Clusters of black gr ules lly present (d gnosti)	N c ts.
V s bl ty f leus.	N t is l le e cept i ld d g t d cysts	Visible e pt when led by gl co- g m s ng y ts More th f n s diag ost c.	Not is bl	Somet mes v bl as light-bl d k.	N ts

TABLE 29.—DIFFERENTIAL CHARACTERISTICS OF THE INTESTINAL AMEBAE
(Normal saline smear)

	E. histolytica	*E. coli*	*E. nana*	*I. bütschlii*	*D. fragilis*
LIVING TROPHOZOITES					
Size (in microns)	6 to 40. Small race ca. 8. Large race: In carriers ca. 14. In dysentery ca. [illegible]	12 to 30. Usually about [illegible]0	6 to 12. Usually about 8	6 to 20. Usually about 10.	6 to 18. Usually about [illegible]
Shape when at rest	Rounded but slightly irregular	Same.	Same.	Same.	Faultlessly spherical (distinctive)
Motility	Pseudopodia tongue-like, protruded with explosive force. Sometimes moves in one direction and in rapid succession, giving rise to a progressive directional crawl. (Forceful and directed; *diagnostic*.) It could form pseudopodia similar to *E. coli* and *E. nana*	Pseudopodia broad (crescent shaped); sometimes budding, sluggishly protruded and lazily withdrawn. Rarely [illegible] sluggish progressive directional crawl.	Pseudopodia small, budding, knob-like, overlapping. Little or no progression.	Same as *E. nana*; never progressive directional crawl.	Th[illegible] leaf-like, fan-shaped, triangular or rectangular or leaf-like with sharp corners or points (diagnostic). No progression.
Endoplasm and its inclusions	Endoplasm clear. R.B.C.'s ingested in the presence of blood, as e.g. in amoebic dysentery (diagnostic)	Endoplasm dirty due to bacteria and food debris. Ingested R.B.C.'s seen very rarely	Same as *E. coli*. No ingestion of R.B.C.'s.	Same as *E. coli*. No ingestion of R.B.C.'s	Cytoplasm thin, ingested bacteria and food bo[illegible]. No ingestion of R.B.C.'s.
Visibility of nucleus	Invisible except in flowing endoplasm during progressive crawl when it may be seen as a dimly outlined ring. In old trophozoites [illegible] nucleus [illegible] visible as a bl[illegible] ring	Almost always visible as a grayish black ring in fresh trophozoites.	Sometimes seen as grayish-blue disc. (Not clear enough to be of diagnostic importance.)	Same as *E. nana*.	Not visible
LIVING CYSTS					
Size (in microns)	5 to 18. Small race about 8. Large race about 12	10 to 30. Average 17	6 to 10. Usually 8.	6 to 16. Usually 10	No cysts.
Shape	Rounded but seldom perfectly spherical.	Same	Rounded, oval, sausage-shaped (diagnostic)	Rounded or oddly shaped: triangular, pear or kidney shaped (diagnostic)	No cysts.
Chromatoid matter	Abundant. Bars with rounded ends or cigar-shaped rods (diagnostic). Present in from 0 to 100%, usually in more than 50% of the cysts.	Scanty. Splinter-like blocks with sharp points (diagnostic). Seldom seen in more than 10% of the cysts	None.	None.	No cysts.
Glycogen	Rarely in sufficient amount to change appearance of cyst.	Young cysts filled with glycogen and muddy cytoplasm.	No glycogen visible.	Majority have well-defined dense glycogen ball slightly refractile, light-blue (diagnostic)	No cysts.
Volutin granules	None.	None.	None.	Clusters of black granules usually present (diagnostic)	No cysts.
Visibility of nucleus	Not visible except in old degenerated cysts	Visible except when concealed by glycogen in young cysts. More than four is diagnostic.	Not visible.	Sometimes visible as light-blue disk.	No cysts

CHAPTER 27

ALLERGY

The clinical state of *allergy* represents a *perversion of the mechanisms of* body defense In this strange disorder the antibody antigen reaction in place of producing immunity and cure effects a widespread tissue change which may be of mild moderate or even fatal import The unhappy result may be systemic as in anaphylactic shock or it may involve only a single structure referred to as the *shock organ* The substance that produces the anaphylactic state is the *anaphylactogen* the response of the cells is the production of *anaphylactic antibody* the noxious product which results from the reaction of anaphylactic antigen and anaphylactic antibody is the *anaphylatoxin* Transfer of sensitivity from one to another animal constitutes *passive anaphylaxis* the nonreactive period which follows an *anaphylactic* shock is the interval of *anti anaphylaxis*

It is a curious paradox in Nature that the most powerful of the available anti infective agents (p 106) is derived from a potentially invasive parasite and that serious and even fatal clinical reactions may result from a perversion of the mechanisms of host defense Further exemplifying the *noxious effects of intended reparative agencies fever is usually a protective* endeavor but *hyperpyrexia* may prove fatal scarring is a phase of a successful inflammatory episode but the cicatricial tissue may so diminish parenchymal function that the patient succumbs in *hepatic cirrhosis* for example to a *cholemia* due to insufficiency of the liver

The Varieties of Allergy —Students of allergy recognize the subdivisions of anaphylaxis and atopy The state of *anaphylaxis* is an acquired characteristic that is observed in the lower animals as well as in man it is caused by only a few allergens which are protein in nature so far as is known

By contrast *atopy* is a hereditary sensitivity to a wider variety of protein *and nonprotein substances Its clinical manifestations seem quite limited* to the human being it may arise from a bewildering number of etiological agents which gain entrance to the tissues by inhalation inunction contact injection ingestion exposure or absorption

Pathogenesis and Mechanism —The pathogenesis and mechanisms of allergy are best exemplified by the anaphylactic phenomenon observed in the laboratory from the injection of horse serum into the guinea pig

The protocol of the experiment involves an initial intravenous or intraperitoneal *injection of horse serum* Following a lapse *of ten to fourteen* days the reinjection of the previously nontoxic horse serum produces the disturbing and at times fatal manifestations of anaphylactic shock The *guinea pig appears nervous it scratches its nose* develops difficulty in breathing due to bronchospasm the pulse rate becomes rapid and convulsive episodes may produce a fatal termination within a few moments

Chiniofon N N R—Chiniofon resembles vioform in its mode of action and effectiveness against fixed and motile amebas Some workers believe it is the best of all amebacides though emetine is unquestionably superior in amebic hepatitis and extra intestinal abscess Likewise emetine is superior to all other amebacides in relieving severe symptoms of acute dysentery

Chiniofon is practically nontoxic in therapeutic doses Occasionally iodism and profuse diarrhea follow its use It should not be employed in the presence of liver disease

Therapeutic Use and Dosage—Because of its low toxicity chiniofon can be used in mass and ambulatory treatment The drug is official in the U S P Chiniofon also is sold as anayodin or yatren

The usual dosage ranges from 0 75 to 1 0 gm (12 to 15 grains) given in tablets or enteric coated capsules It is preferable to begin with 0 25 gm (4 grains) t i d to minimize the diarrhea which sometimes occurs at the beginning of therapy The drug is generally given with meals in divided doses three times a day Children receive amounts proportional to their ages Chiniofon may also be given as a retention enema (6 gm [90 grains] in 300 cc warm water) nightly for as long as ten nights During this time the oral dose should be diminished to 0 5 gm (7½ grains) or less per day

Carbarsone N N R—Carbarsone, an organic pentavalent arsenical, has an amebacidal activity similar to that of the oxyquinoline drugs differing from emetine as they do Its index of toxicity is low and it acts fairly effectively on amebas in the submucosa and on the mucosa and free in the intestinal contents

Administration and Dosage—Carbarsone N N R is available in 0.5 to 0 25 gm (7½ and 4 grains) tablets 0 25 gm (4 grains) gelatin capsules 2 gm (30 grains) vials and 0 12 gm (2 grains) suppositories for rectal use

A course of carbarsone consists of 0 25 gm (4 grains) given twice a day for ten days and repeated if necessary at ten day interval Dosage for children is determined on the basis of weight

A retention enema of 1 per cent carbarsone in 2 per cent sodium bicarbonate may be useful The enema is best given on alternate evenings (after a preliminary cleansing enema) until five have been retained over night Oral medication is omitted during rectal treatment

Toxicity of Carbarsone—*Skin rashes edema slight nausea* and *vomiting* and increased *diarrhea* are the only common side effects of carbarsone *Visual disturbances have rarely been reported* Because of these side effects mild though they be carbarsone cannot be used for mass treatment Patients must be supervised during therapy and preferably should remain in bed The drug is not used for patients with kidney or liver disorders

Other Arsenical Amebacides—Acetarsone and treparsol have also been employed as amebacides but are inferior to carbarsone Both are more toxic There is no good reason for their use

Combined Treatment—The United States Navy recommends the following course for the treatment of acute and chronic amebic dysentery *Emetine hydrochloride* is given subcutaneously in 1 grain dosage daily for five days On the *third day of emetine therapy carbarsone* is given orally three times a day in 4 grain dosage This is continued for seven days or five days beyond the cessation of the emetine After a treatment holiday

of the diluted biologic agent is instituted and 1 cc of epinephrine chloride is added to each 100 cc of infusate

Anaphylactic Shock—The third and most serious type of serum sickness is that which occurs when serum is injected into an individual who is naturally sensitive to horse serum but who may never have received serum before This primary type of serum sickness resembles anaphylactic shock in the lower animals and may be fatal

Human anaphylaxis differs from anaphylaxis in the lower animal only in that an immediate shock may follow the first injection of antigen in an individual who has an hereditary atopy

Human anaphylaxis presents an indelible and dramatic clinical syndrome Immediately upon the introduction of the intended therapeutic agent the patient develops the shock symptoms exemplified by the experimental animal (p 547) In less time than is consumed by the verbal description the victim may succumb with convulsive episodes due to asphyxia from the intensity of the bronchospasm In more fortunate circumstances recovery takes place within a measurably short time that seems to the observer like an eternity

Drug Atopy—Atopy may result from the administration of a variety of drugs some of which are not protein in nature Drug atopy differs from *drug poisoning* in that the symptoms are unlike the pharmacodynamic effects and are unrelated to the amount of the administered dose (Fig 9[illegible])

The commoner drug atopens are acetylsalicylic acid antipyrine arsenic sulfonamides insulin quinine morphine bismuth ipecac phenolphthalein oil of cade veronal and cocaine and its substitutes

Drug atopens may produce their effects through inhalation ingestion contact or injection The contactual manifestations are much the most common and are grouped as *dermatitis medicamentosa* (p [illegible]) Systemic symptoms such as hyperpyrexia and *remote organ effects* such as bronchospasm or angiospasm also may be observed

The diagnosis of drug atopy rests on the history Skin tests are of questionable value the skin may exhibit multiple sensitivities to preparations of no etiologic significance while a test reaction to an offending atopen may produce a protracted and serious dermatitis

Contactual Atopy—Contact dermatitis is one of a large group of dermatoses previously classified under the meaningless term of eczema More detailed descriptions are given in the section on Dermatology (p 3330) It is sufficient to emphasize here that the vast majority of cases of contact dermatitis result from *occupational exposure* (p 3332) or the use of *cosmetics* (p [illegible]138) The first of these rarely offers a diagnostic problem to the physician since the worker is usually aware of the hazard and often suggests the possibility to his practitioner Cosmetic dermatitis however is an individual problem whose recognition may not be accepted by the patient and may in fact be actively opposed and resented The more frequent cosmetic culprits include *lipstick nail polish* and *hair lacquers*

Pollen Atopy—Pollen atopy is encountered during the periods of plant fertilization when the male element is wind or insect borne to the pistil or female element Of wind pollinated plants a comparatively small number are capable of producing an *inhalation allergy* In the United States trees pollinate from March 15 to May 15 grasses from May 1 to July 1

SOUTH AMERICAN TRYPANOSOMIASIS (CHAGAS DISEASE)

Chagas disease is found chiefly in Brazil but may also be encountered in other countries in the northern portion of the South American continent The causative agent *Trypanosoma cruzi* is morphologically similar to

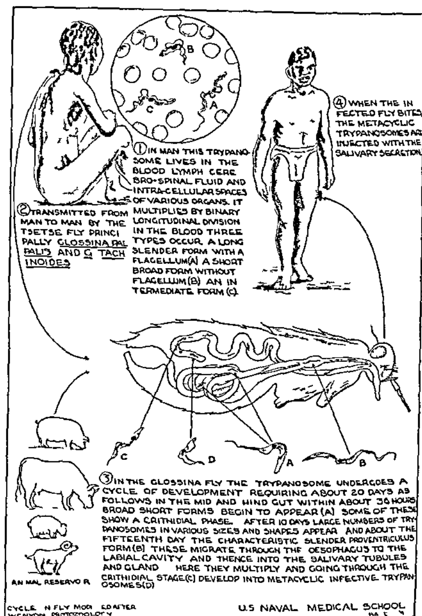


Fig 88—Life cycle of trypanosoma gambiense

other trypanosomes but in the tissues it takes the forms of a leishmania like parasite The infection is transmitted by several varieties of biting insects The clinical disease may be acute or chronic Children are most frequently infected

of the diluted biologic agent is instituted and 1 cc of epinephrine chloride is added to each 100 cc of infusate

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Prophylactic chemotherapy is suggested with naphuride A single injection of 1 gm (15 grains) gives protection for three months

LEISHMANIASIS (KALA AZAR, DAUKALIN)

The clinical entities of kala azar, Oriental sore and American leishmaniasis are produced by closely related strains of the protozoal leishmania The systemic manifestations of kala azar are described here Cutaneous leishmaniasis is discussed in the chapter on the *Tegumentary Disturbances* (p 3317)

Kala azar is characterized by *enlargement of the liver and spleen* progressive emaciation fever and anemia It occurs particularly in India China countries bordering along the Mediterranean Sea and Africa It is most common in children Synonyms include dum dum fever tropical splenomegaly and ponos

ETIOLOGY

The transmission of kala azar is generally thought to occur through the *Phlebotomus* or *sandfly* There is an invasion of the blood stream with localization of the parasite in the cells of the reticulo endothelial system particularly the spleen liver lymph nodes and bone marrow These cells phagocytize the parasite and eventually burst liberating the organisms which are then phagocytized by other cells As a result of this process tremendous enlargement of the spleen occurs Anemia results from crowding of the bone marrow with the parasites

CLINICAL MANIFESTATIONS

The clinical course is marked by irregular and recurrent bouts of *fever* with *progressive enlargement of the spleen liver and lymph nodes* *Hemorrhages* are common from the nose and intestinal tract Profound secondary anemia occurs There is an elevation of serum globulin and a reduction of albumin Leukopenia is the rule Untreated it is said that the case mortality is as high as 90 per cent within two years of onset Death usually results from intercurrent infection The Indian name of *daukalin* refers to a characteristic double daily rise of temperature

DIAGNOSIS

The diagnosis is made by finding the parasites in stained smears of the tissues Needle aspiration of the liver spleen or sternal bone marrow is performed and the tissue juice or blood is fixed stained and examined for *Leishman Donovan bodies* (Fig 89) It is also possible to culture the parasite from tissue juice A presumptive diagnosis based on *increase in serum globulin* depends on a precipitate forming when an excess of distilled water is added to blood In the test 0 02 cc of blood is mixed with 0 6 cc of distilled water After five minutes a haziness develops which may also be produced by adding 1 drop of 30 per cent formalin to 1 cc of clear serum This test is known as Napier s aldehyde formol gel reaction for kala azar

TREATMENT

The trivalent compounds of antimony such as *fuadin* (stibophen) are relatively ineffective in the treatment of visceral leishmaniasis The effective preparations are the *pentavalent antimony compounds* such as

Food Atopy—Atopy resulting from the ingestion of food is a definitely recognizable clinical entity. The most common offenders include strawberries, fish, wheat, eggs, milk, chocolate, tomato, peas, beans, potato and the meats, particularly pork.

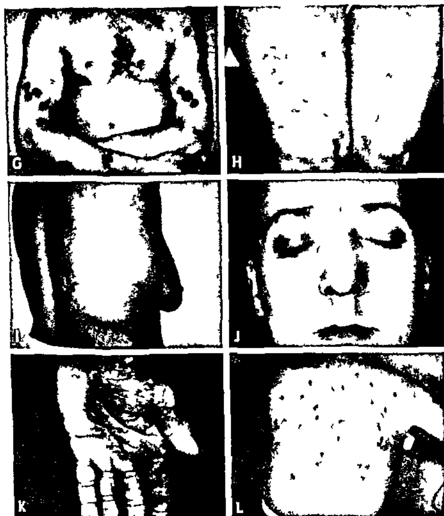


Fig 92 (continued) —*G* Drug atopy Dermatitis medicamentosa from phenolphthalein taken as cathartic *H* Drug atopy Dermatitis medicamentosa from phenobarbital taken as sedative *I* Drug atopy Dermatitis medicamentosa from arsenic injections for syphilis *J* Contactual atopy (occupational) From refrigerating gas *K* Contactual atopy (occupational) From tar *L* Trichophytid from ringworm of feet

The familiar clinical examples of food atopy include attacks of *urticaria* and *angioneurotic edema* from strawberries and fish. The *infantile eczemas* result from the ingestion of milk and eggs. Less definite are such disturbances as a coated tongue, heavy breath, abdominal distention, eructations, sour stomach, epigastric heaviness, pyrosis, nausea, vomiting in

disease of the central nervous system and cardiac or skeletal musculature especially in children Infants may suffer repeated convulsive seizures and exhibit evidences of mental deficiency, if they survive Focal disseminated chorioretinitis is a frequent and suggestive finding Irregular small calcifications may be visible on skull x rays Specific complement fixation antibodies are demonstrable See *Differential Diagnosis of Nonsuppurative Encephalomyelomeningitides* (p 442)

The toxoplasma may on rare occasions produce adult infections Reported instances have shown manifestations of severe *encephalomyelitis* and the organism has been recovered from body fluids and exudates The parasite typically resides within mononuclear and epithelioid cells nerve cells muscle fibers the endothelial cells and capillaries the polymorphonuclear and the eosinophilic leukocytes Inoculation of guinea pigs with infected material produces characteristic lesions which may be verified by biopsy

The *prognosis* of the known infection is grave and some hope has been advanced from the demonstration that the soluble *sulfonamides* control experimental disease Certainly if the practitioner encounters a toxoplasmosis he is thoroughly justified in giving large doses of *sulfadiazine* and may even reinforce his therapeutic attack with *penicillin* and *streptomycin*

Laboratory tests suggest that there is the possible development of a protective faction

and psychogenic influences Most atopic individuals are tense and high strung the allergic manifestations are relieved by sympathomimetic drugs such as epinephrine certain of the disturbances such as bronchial asthma yield to psychotherapy particularly by methods of psychoanalysis (p 1378)

The clinician is familiar with the production by purely psychogenic mechanisms of manifestations of allergy He observes that many attacks of *urticaria angioneurotic edema* and *bronchial asthma* are precipitated by emotional disturbances often these disturbances abate when peace is restored and recur when conditions again become disquieting

CLINICAL MANIFESTATIONS

The clinical manifestations of human allergy are listed as definitive or probable eventualities More exact descriptions of each syndrome are given in the material which deals with the individual organ since it is in this way that the problem is presented to the practitioner

DEFINITIVE MANIFESTATIONS OF HUMAN ALLERGY

Manifestation	Allergen
Anaphylactic Shock (p 549)	Serum digestants (egg milk)
Serum Sickness (p 48)	Serum
Seasonal Vasomotor Rhinitis (p 2097)	Pollen
Nonseasonal Vasomotor Rhinitis (p 2098)	Bacteria digestants
Bronchial Asthma (p 101)	Pollen bacteria digestants psychogenic
Eosinophilic Pneumonia (p 2104)	As asthma
Vernal Conjunctivitis (p 16 1)	Pollen
Phlyctenular Keratoconjunctivitis (p 16 0)	Pollen
Atopic Dermatitis (Eczema) (p 334?)	Digestants
Contact Dermatitis (Venenata) (p 3330)	Drugs chemicals industry cosmetics plants (poison ivy)
Dermatitis Medicamentosa (p 33)	Drugs chemical cosmetics
Urticaria and Angioneurotic Edema (pp 3345 3349)	Serum digestants drugs bacteria physical energy psychogenic
Disseminated Neurodermatitis (p 3343)	Psychogenic digestants chemicals
Ids (pp 328 326 3 90)	Syphilids tuberculids dermatophytids

POSSIBLE CLINICAL MANIFESTATIONS OF HUMAN ALLERGY

Manifestation	Allergen
Migraine and Epilepsy (pp 1 06 151)	Digestants psychogenic
Ménière's Disease (p 1486)	Digestants psychogenic
Gastric and Intestinal Neuroses (p 1 67)	Digestants psychogenic
Pruritus Ani (p 1916)	Digestants psychogenic
Erythema Nodosum Erythema Multiforme (p 33 7) and Purpura (p 3423)	Bacteria
Atrophic Arthritis (p 2910)	Bacteria digestants
Sympathetic Ophthalmia (p 1569)	Lens protein
Chronic Glomerulonephritis (p 23 9)	Beta hemolytic streptococcus
Thrombo-angiitis Obliterans (p 10 9)	Tobacco ry
Periarteritis Nodosa (p 1027)	?
Angiospasm (p 90)	?

various blood flukes, the *Schistosoma hematobium* *S mansoni* and *S japonicum*

Geographical Distribution —The geographical distribution of the Schistosomes is as follows

S haematobium — *Africa* (Nile Valley Ethiopia Sudan East Coast, Belgian Congo, Nigeria Lake Chad, Madagascar Mauritius Reunion)
Asia (Palestine Syria Iraq Mesopotamia, Arabia)
Australia?

S mansoni — *Africa* (Nile delta Upper Sudan East Coast North Rhodesia, Belgian Congo Senegal Fr Guinea, Lake Chad Madagascar Sierra Leone)
South America (N Brazil Venezuela, Dutch Guiana)
Caribbean Area (Antigua, Guadeloupe Martinique St. Lucia, St Kitts Nevis Montserrat, Vieques Puerto Rico)

S japonicum — *China* (Yangtze basin Coastal area)
Japan
Formosa
Philippines
Celebes

Life Cycle of the Schistosomes.—The blood flukes live in the *venous plexuses* around the bladder the colon or the mesenteric veins of the small intestine At these sites the *eggs* are laid and make their way into the walls of the blood vessels the lumen of the bladder or the intestine The mature eggs are passed with the *urine* or *stool* and they hatch almost immediately if conditions are favorable Within a period of thirty two hours the *ciliated larvae* (*miracidia*) which hatch from the egg of the fluke attack one of the groups of *snails* which act as *first intermediate hosts*

Within the snail two generations of *sporocysts* are produced finally giving rise to the *cercaria* a larva which possesses a mouth pharynx gut and tail In about a month the cercariae are ready to leave the snail which may or may not die as the result of the infestation It is estimated that a single miracidium may have formed 100 000 to 200 000 cercariae

The cercariae released by the snail remain infective in water for one to three days During this period they attack man by *penetrating the skin* The cercariae discard their tails and are carried by way of the blood and lymph channels to the liver where they develop into mature adults in six to eight weeks The cycle is completed by the migration of these adults to the venules in the walls of the gut or bladder

Clinical Manifestations —The earliest clinical manifestation of schistosomiasis is the appearance of a *papular dermatitis* at the site where the cercariae have penetrated the skin Four to eight weeks later at the time that the adult forms develop in the liver constitutional symptoms are observed including *fever eosinophilia hematuria* and an eruption of *giant hives* Later when the organisms have migrated to the venules in the walls of the gut or bladder the patient develops manifestations of a chronic dysentery or *urinary symptoms* secondary to the development of intestinal or *vesical ulcers* and *papillomas* *Urinary fistulae* and *calculi* may occur in association with a *hepatosplenomegaly* (pp 1129 1973)

Diagnosis —The suspicion of the presence of schistosomiasis is confirmed by the demonstration of the eggs in the urine or feces The last few drops of a micturition should be specially examined Cystoscopy may reveal multiple minute calcified bodies or sandy excrescences from which specimens may be obtained

Treatment

Schistosomiasis is best treated by intramuscular injections of fuadin (stibophen), which is a 6 3 per cent solution of a *trivalent organic antimony*

teristically few constitutional symptoms and no evidence of invasive inflammation such as fever leukocytosis or rapid sedimentation rate

ALLERGY TESTS

Practitioners of medicine are becoming increasingly aware of the frequent presence of allergic phenomena in clinical practice It is estimated that 2 per cent of the population of the United States is afflicted with allergy of the upper respiratory tract and about 10 per cent with other types of sensitivity

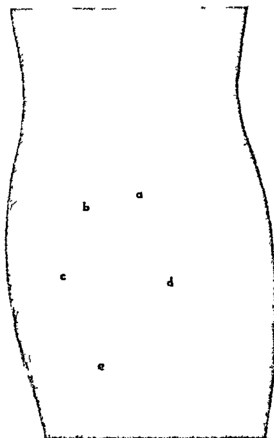
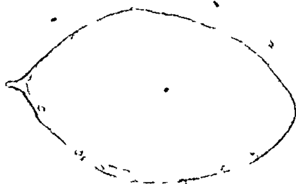


Fig 94 —Skin reactions after scratch tests with allergenic extracts *A* Negative or control *B* Doubtful *C* Slight *D* Moderate *E* Marked

Tests may be performed in the office laboratory and by the clinical pathologist The cooperation of the pharmaceutical manufacturers has made available preparations of allergens for testing and treatment by desensitization

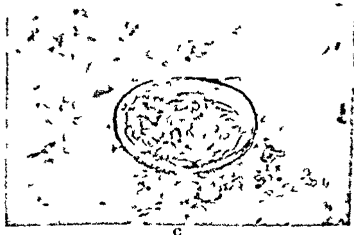
Allergy tests are performed by (1) the *contact* or *patch* method (2) *instillation* into the conjunctival sac (ophthalmic test) (3) the *scratch*



A



B



C

Fig 90—*A* Ovum of *S haematobium* in urine Note terminal spine × 450 *B* Ovum of *S mansoni* in feces Note lateral spine × 450 *C* Ovum of *S japonicum* in feces Note absence of spine × 450

Courtesy of Sharp and Dohme Seminar May 1944

and itching This can be controlled by the instillation of 1 or 2 drops of epinephrine hydrochloride (1 1000)

Scratch Test (Routine)

The scratch method is commonly employed in testing for sensitivity to the *pollens* and *alimentary allergens* A linear abrasion about ¼ inch long is made with a needle or a scalpel This must be sufficiently superficial so that no blood is drawn The extract to be tested is rubbed into the abraded surface permitted to dry and compared with a control scratch that has not been exposed to the allergen (Fig 94)

Readings and Interpretation—The result is read at the end of twenty to thirty minutes The *negative reaction* will appear little altered from the control A *questionable positive response* will consist of a slight elevation and induration the areola measuring approximately 1 cm in excess of the control and causing little or no itching A *genuinely positive reading* is a wheal arising in ten to thirty minutes and remaining for thirty to sixty minutes The reaction should be at least the size of a dime elevated and indurated with a certain amount of itching and perhaps some pseudopodia formation When the reaction is particularly marked the area involved may be extremely large and the swelling and itching so intense as to require therapy with a vasoconstrictor It is possible to evoke systemic responses from the tests which are employed with the greatest caution in those who have violent allergic manifestations such as bronchial asthma

Intradermal Test

The intracutaneous injection method is particularly used for the testing of the soluble allergens made from various invading micro-organisms The skin is cleansed gently with alcohol No other disinfectant should be used *The skin is dried carefully so that a false reaction is not produced* by the inadvertent injection of alcohol The intracutaneous injection is made with a 27 gauge ⅜ inch needle attached to the tuberculin type of syringe The needle is inserted between the layers of skin and is placed at a most oblique angle to the skin which is drawn taut by the fingers of the free hand The *volar surface* of the forearm is the best site for injection The amount of substance injected should not exceed 0 2 cc If the injection is correctly made a small elevation resembling a mosquito bite will appear Control tests should be done with 0 2 cc of saline solution using an identical site on the opposite arm If multiple tests are done they should be spaced 2 inches apart (Fig 95)

Readings and Interpretation—The intracutaneous injection test is read in ten to thirty minutes at twenty four and forty eight hours and again at the end of a week An *immediate markedly positive reaction* consists in the production of a wheal showing pseudopodia with a surrounding area of erythema The wheal is raised and indurated and may itch Lesser degrees of reaction approach the appearance of the control No reaction should be read as positive unless it is more than double the intensity of the control reaction

The *late positive reaction* is a tense red papule at least double the size of the control The induration persists *for several days after which* the skin exfoliates leaving a pigmented area in the more intense instances

Diagnosis —The definitive diagnosis of trichinosis is established by the demonstration of the parasite in muscle obtained by biopsy or in spinal fluid A *skin test* using an antigen derived from the larvae appears to have considerable diagnostic value *Complement fixation* and *precipitin* tests have also been perfected

DIFFERENTIAL DIAGNOSIS OF

Eosinophilia

In most instances eosinophilia suggests the presence of circulating allergen It is most commonly encountered in the familiar allergies and in infections and infestations characterized by the introduction into the body of a foreign protein

CAUSE	DIAGNOSTIC FEATURES
Allergies	In hay fever bronchial asthma and eosinophilic pneumonia (p 2104) History of sensitivity Eosinophils in nasal secretions and sputum Symptomatic relief from epinephrine Also in periarteritis nodosa (p 1027) with fever hypertension renal insufficiency and cutaneous nodules which show characteristic changes in biopsy
Blood Dyscrasias	In polycythemia vera and myeloid leukemia and in pernicious anemias treated with raw liver Diagnosed by hemogram
Dermatoses	In cutaneous allergies of urticaria angioneurotic edema and atopic dermatitis (eczema) In descriptive dermatoses such as dermatitis herpetiformis pemphigus mycosis fungoides and psoriasis
Eosinophilic Granuloma of Bone	Especially in skull of children Tendency to spontaneous cure Get x ray and biopsy (p 2843)
Familial	Occasionally encountered on hereditary basis
Hodgkin s Disease	Lymphadenopathy splenomegaly and irregular but progressive fever (p 1138) Get biopsy and note response of granulomas to x ray
Intestinal Helminthiasis	With ova parasites or segment in stool Skin test and complement fixation in echinococcosis (p 1983)
Systemic Helminthiasis	Hemic distomiasis and trichinosis In former identify ova in stool or urine (p 1894) In latter note myalgia edema beneath eyes positive skin test (p 541) and complement fixation (p 59)

The presumptive diagnosis of trichinosis rests upon the history of the ingestion of infected pork and an associated enteric fever characterized by eosinophilia muscle pains and facial edema The *typhoidal fevers* are usually suspected but there are no confirmatory laboratory tests (p 233)

Treatment —The treatment of trichinosis is entirely symptomatic Purging and the use of vermifuges probably do more harm than good since

Passive Transfer Tests (Prausnitz Kustner)

The Prausnitz Kustner test is used to indicate the presence of *anti bodies* (reagins) in the blood Under sterile precautions blood is obtained from the patient and allowed to clot The serum obtained is then injected intradermally in several places in 0 1 cc amounts into a normal *individual* in whom the antigens have given no previous reaction The following day scratch tests are performed at the sites of the serum injections using the suspected protein antigens If antibodies were passively transferred from the blood serum of the patient to the normal experimental control a positive reaction will ensue

The passive transfer method of testing is used chiefly for experimental study It has practical application in children who are difficult to test and in those patients who suffer from a dermatitis so extensive as to leave little or no normal skin available for testing Occasions of this sort arise principally in *atopic dermatitis* (disseminated neurodermatitis) and a volunteer may be sought among friends or relatives of the afflicted Needless to say in self protection the physician should request a waiver after a complete explanation of the procedure to patient and volunteer alike

Practical Uses of Allergy Tests

Pollens.—The scratch tests for pollen sensitization are very satisfac tory Most large manufacturers supply testing sets based on the time of pollination in the various geographical areas This type of testing will be found highly accurate and highly satisfactory There is no reason why it cannot be done by the practitioner Treatment sets may be purchased for immunization of the sensitive

In the United States *hay fever* or *vasomotor rhinitis* (p 2097) occur ring during April May June and July most likely results from sensitiza tion to June grass orchard grass sweet vernal grass red top timothy plantain or tree pollens From August 1 until frost the sensitization is almost universally caused by the common or giant ragweed and Russian thistle (Fig 96)

Alimentary Allergens —The number of alimentary allergens is legion The performance of multiple tests may lead to confusion and even to ridicule Many patients respond negatively to allergens to which they are known to be sensitive and positively to foods they can eat with impunity Because of the unreliability of the skin as a shock organ in alimentary allergy it has seemed wise to limit testing to intracutaneous tests for sensitivity to milk wheat and eggs (p 558) since most remedi able alimentary allergies are caused by these substances

The accuracy of the skin test may be checked with the most reliable of all diagnostic procedures—the method of trial and error—executed by observing the clinical effect of ingestion of the suspected allergen *Elimina tion diets* (p 562) which exclude certain substances are of diagnostic and therapeutic value

Serum —The detection of serum sensitivity is of the greatest clinical importance Since there may be sensitization to horse serum as a result of prophylactic and therapeutic administration of antitoxin (p 86) biologicals should not be administered without ophthalmic or skin test

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In testing for bacterial allergy, the suspected organism is isolated cul tured and grown A vaccine is prepared a filtrate obtained and a skin test done with the filtrate

The *positive tuberculin test* is an example of the bacterial allergy The patch method of testing may be supplemented by the *intracutaneous test* (*Mantoux*) which uses a solution of Old Tuberculin diluted with saline In testing a new patient old tuberculin is diluted 1 100 000 and 0 1 cc injected into the skin A positive reaction appears as a red wheal in from forty eight to ninety six hours If the reaction is negative the dilutions are reduced to 1 10 000 1 1000 and if necessary 1 100 Instead of old tuberculin which varies in composition a *purified protein derivative* (P P D) dispensed by the National Tuberculosis Association may be used

Skin tests utilizing the same principle have been devised for the diagnosis of other infectious diseases (p 61) such as *lymphopathia venereum* (Frei test) *brucellosis* (Huddleson test) *echinococcus dis ease* and *trichinosis*

Interpretation of Allergy Tests

To evaluate the allergy tests correctly certain limitations must be recognized

Allergy may be present with a normal skin reaction It is quite possible to obtain *false negative reactions* particularly in the case of alimentary allergens In this instance the intestinal tract may be sensitized to the offending substance which is innocuous to the skin In addition to *differen tial organ sensitivity* there may be local differences in cutaneous hyper sensitivity one area of skin failing to react to an allergen which affects another area due to altered conditions such as exposure to sunlight the presence of sweat and macerated epithelium

Clinical sensitivity may be absent with a positive test The skin may be unusually sensitive and give a *false positive reaction* when the clin ical symptomatology in other organs is completely unrelated to the posi tive test Again the particular patient may have been sensitized some time in the past retain that sensitization yet not suffer clinically as the result of the particular allergic state Tuberculin reaction for example does not indicate that the patient is suffering from tuberculosis merely that the patient at some time in his life has been sensitized to the protein of the tubercle bacillus with or without clinical manifestations In such in stances the positive test is misleading

The crux of the matter is the concept that the skin test like every other laboratory procedure *is a clinical finding to be interpreted by the physician It is not of absolute value unless the clinical findings and the course of events are corroborative*

Reference to the Allergist

The foregoing tests would seem to be the limit to which the general practitioner should venture in the investigation of allergic phenomena The specialized allergist should be consulted

1 If the above mentioned tests are insufficient or misleading
2 If the skin tests are equivocal or dubious
3 If the indicated therapy has not proved successful

Autopsy discloses congestion of all organs acute pulmonary emphysema multiple punctate hemorrhages and incoagulability of the blood Should the animal recover from the anaphylactic episode *it remains nonreactive or anti anaphylactic* for several weeks after which it is again sensitized and may again develop anaphylactic shock upon reinjection of the antigen

The anaphylactic antibody may be *passively* transferred from one to another animal or from mother to offspring Its presence is demonstrable on isolated tissue when a strip of uterus suspended in a neutral bath develops spasmodic contractions if the specific antigen is added to the diluent In these experiments the horse serum is the *anaphylactic antigen* the substance which is passively transferred is the *anaphylactic antibody*

In the lower animal anaphylaxis does not occur spontaneously it is not hereditary the anaphylactogen is protein in nature sensitivity is specific and usually is single rather than multiple The anaphylactic reaction may be mild violent or fatal It may involve the bronchial musculature the wall of the pulmonary artery or the liver cells but there is no method of determining why these variations occur or of predicting their occurrence

The most acceptable hypothesis for the phenomenon of anaphylactic shock is a cellular *injury resulting from the antigen antibody* reaction In this process the cells liberate *histamine* or a *histamine like substance* (p 713) which is responsible for the explosive and violent symptoms

ETIOLOGY

Human allergy may be caused by a wide variety of substances both protein and nonprotein These include serums drugs contactual substances pollens foods bacteria and physical and psychogenic agents

Serum Atopy—The most commonly recognized forms of human allergy are those produced by the administration of horse serum (p 84) Delayed and accelerated types of *serum sickness* may result as well as the more violent manifestation of anaphylactic shock

Serum Sickness—Serum sickness may occur in the normal individual eight to twelve days after the administration of horse serum It is characterized by elevation of temperature urticarial dermatoses lymphadenopathy and arthropathies Symptoms persist for from three to seven days and then disappear wholly and completely Serum sickness in the normal individual cannot be prevented it may occur in the presence of negative skin and ophthalmic tests

Accelerated Serum Reactions—Those who have previously received serum may develop an immediate or accelerated type of serum reaction which is commonly more severe than ordinary serum sickness and which may prove fatal The accelerated type of acquired serum allergy occurs after an interval of only twenty four to forty eight hours and simulates ordinary serum sickness except that it is more intense

The patient who gives a history of having previously received an injection of serum is regarded as a candidate for an accelerated serum reaction even though skin and ophthalmic tests are normal Subcutaneous desensitization (p 86) is always required before the intravenous administration of serum If skin or ophthalmic tests are positive or the patient gives a personal or familial history of atopy serum therapy is best withheld unless the indications are urgent If the need is great a slow intravenous drip

THERAPEUTIC TRIAL

The actual diagnosis of an allergy is not established until the thera peutic trial proves the correctness of the assumption The patient with a common cold may have a family and personal history of allergy a positive skin reaction and demonstrable passive transfer tests none of which are pertinent to the presenting complaint

TREATMENT

The treatment of allergy consists in elimination or avoidance of the offending allergen substitution desensitization palliation pharmaco therapy immunotherapy and psychotherapy

Elimination —Certain of the nonessential allergens may be removed from the environment or diet of the patient It should be possible to get along without cow s milk wheat eggs chocolate a horse a dog pillows contain ing goose feathers lipstick nail polish and nonessential drugs such as acetylsalicylic acid phenolphthalein or phenobarbital

Substitution —Allergens that are of essential importance may be replaced by very similar products Children who are sensitive to cow s milk are tried with *goat s milk* or the milk that is prepared from *soy beans* (p 2754) other *cereal grains* are utilized to replace wheat the fastidious patient may use another brand of *lipstick* or *nail polish* offending drugs are dis continued in favor of preparations with similar pharmacological action

Desensitization —For purposes of desensitization the antigen may be given orally or by parenteral injection

Oral Method—For oral desensitization the offending substance is dis solved in a large quantity of water For example a teaspoonful of milk is made up to a volume of two quarts with water An initial desensitizing dose is as little as a half teaspoonful When a full glass of this mixture is tolerated the dilution is lessened until finally drop dosage of the pure substance is ingested with the greatest caution

Intracutaneous and Subcutaneous Method—Intracutaneous and sub cutaneous desensitization using repeated injections of the diluted allergen are particularly useful in the treatment of sensitivity to the pollens and other inhalants such as dust orris root and dander and certain of the ingestants such as egg milk or wheat

The *initial* dose to be employed for desensitization is 0 1 cc of that dilution which produces only a slight skin reaction The dose is repeated at five to seven day intervals the amount of injected allergen is slowly in creased depending upon the patient s reaction until 1 cc is administered At this point a dilution of ten times the strength is made up the initial dose of the new and stronger dilution is 0 1 cc or the equivalent of 1 0 cc of the previous mixture The patient must not leave the office for twenty minutes after any injection Epinephrine solution is kept readily available for the treatment of constitutional symptoms Increase in dosage is deter mined solely on the basis of the reaction to the previous injection

Pollen Desensitization—Pollen desensitization is accomplished by pre-seasonal coseasonal or perennial methods In prophylactic or *preseasonal treatment* the patient institutes therapy at least three months before the expected pollination Commercial sets with diluted antigen are available. An attempt is made to give fifteen to twenty doses of the antigen at four

and weeds from August 1 to October 1 The weeds produce the greatest number of sufferers from atopic or *seasonal vasomotor rhinitis* (*hay fever*) and *bronchial asthma* *Ragweed* is the commonest offender followed by *timothy* and *June* and *Bermuda grasses* Tree pollens rarely cause difficulty



Fig 99—*A* Atopic neurodermatitis (eczema) in adult female Probably psychogenic *B* Atopic dermatitis (eczema) in child Of digestive etiology *C* Contactual atopy from cosmetic (lipstick) *D* Contactual atopy from wearing apparel (hatband) *E* Contactual atopy from occupational contact with cosmetic (hair-dye) in beauty shop operator *F* Contactual dermatitis from drug (sulfathiazole ointment)

The diagnosis of pollen atopy is made from the history and the results of the *skin tests* (p 557) The latter are not always completely reliable An occasional negative response occurs with definite clinical atopy more frequently a positive response is noted in an individual without clinical symptoms

of active discomfort sedative drugs (p 3837) are utilized during the day and a *hypnotic* (p 3837) is advised at bedtime

Drug Therapy—Drug therapy accomplishes symptomatic relief of the local disturbance The patient may be given instillations or systemic doses of *epinephrine* (p 3877) or ephedrine (p 3880) the latter combined with phenobarbital is also given orally *amphetamine sulfate (benzedrine)* is available for inhalation ingestion or as intranasal drops *atropine tablets* are swallowed or the solution is injected subcutaneously *belladonna* (p 3875) is given by mouth or in rectal suppositories *stramonium leaves* (p 3875) are smoked in the familiar asthma cigarettes *demerol* (p 3863) gives promise of considerable relief without the dangers attributable to the opiates *aminophylline* (p 3867) is extremely useful in the control of bronchospasm when given intravenously the injection of *calcium salts* particularly the gluconate (p 603) is of occasional value in the relief of an urticaria or an asthma Doses of *iodides* and *nitrites* seem ill advised and their continuance is a holdover from bygone days

The use of the *narcotics* particularly in asthma is approached with some hesitation Often the asthmatic is sensitive to morphine and exhibits the cat and/or frog reaction (p 3858) under which circumstance only harm results There are times however particularly in status asthmaticus when the use of a narcotic cannot be avoided If it is possible a first attempt at relief is made with *demerol* later *papaverine* is employed intravenously in doses of 0 06 to 0 12 gm (1 to 2 grains) the inclusion of *hyoscine hydrochloride* 0 54 mg (1/120 grain) is advocated for synergistic effect In desperation it may be necessary to use *morphine* or *dilaudid* or to induce complete anesthesia with *sodium pentobarbital* given intravenously *avertin* instilled into the rectum or large doses of *paraldehyde* injected intravenously swallowed or instilled into the lower bowel in a starch paste

Immunotherapy—In bacterial allergies cultures are made and *autogenous vaccines* (p 77) are administered sometimes with gratifying results

Surgical Measures—An important principle in the therapy of allergy is the eradication of *foci of infection* particularly in the nose and throat

In the treatment of *status asthmaticus* the *bronchoscopist* occasionally performs a life saving procedure by the removal of mucous plugs and casts from the larger bronchi This form of therapy is a procedure of desperation and is not to be attempted except by the experienced expert

Psychotherapy—Reference has been made previously to the concept that the allergic states are related to psychosomatic manifestations Mindful of this the practitioner is entitled to exert his *psychotherapeutic influences* using nontechnical measures (p 1316) If *psychoanalytic treatment* is available and within the means of the patient this form of approach is seriously considered

testinal cramps, mucous colitis, pruritus ani, migraine, epilepsy, Meniere's syndrome, vertigo, transitory attacks of aphasia and hemiplegia, or angiospasms.

There is no uniformity of opinion concerning the frequency of food allergy. The enthusiasts insist that its incidence approximates 30 per cent of all persons, whereas many experienced clinicians aver that they rarely see a genuine example. The truth probably lies somewhere between these extremes.

The diagnosis of food atopy rests on the *history* and therapeutic tests with *elimination diets* (p 562). *Skin tests* are unreliable and misleading: the skin may not be sensitized to an offending digestant; there may be false positive reactions to foods that are eaten with impunity.

Bacterial Atopy.—The introduction of living or dead bacteria may evoke a variety of tissue responses. These include the stimulation of protective antibodies, the state of anaphylaxis, a hyperpyrexia employed in non-specific protein therapy, or local or focal inflammatory processes in sensitized shock tissues. The last of these are best exemplified by the diagnostic reactions (p 559) that follow intracutaneous injections of specific bacterial proteins (tuberculin, Frei antigen). In addition to their diagnostic importance, these responses have theoretical significance since they may explain certain of the systemic manifestations in tuberculosis, scarlet fever and rheumatic fever. In these diseases involved tissues show no evidence of the presence of the causative bacteria despite the specificity of the lesions.

Bacterial allergy, in our opinion, is of important significance in the pathogenesis of *nonseasonal vasomotor rhinitis* (p 2098). This affliction most often is the result of sensitivity to a living invader whose habitat is the mucous membrane of the nasal passage or its accessory sinuses. Bacterial atopy may exist independently, but more frequently it is associated with seasonal hay fever (p 2097). A vicious cycle is established in which tissue swelling at the time of pollination favors the onset and perpetuation of bacterial infection. The latter in its turn produces sufficient local injury so that the clinical manifestations of the inhalant are prolonged and intensified.

Bacterial allergy is capable also of setting up distant foci of inflammation. The more common sites for the nesting of the offending organisms are the *periapical areas* of the teeth, the mucous membranes of *nose* and *nasal accessory sinuses*, *tonsils*, *gums*, *prostate gland*, *deep urethra*, *fallopian tubes* and *gallbladder*.

The clinical manifestations of focal infection include *general malaise*, low grade *pyrexia*, *myalgias*, *neuralgias*, *mononeuropathies* (p 1480), *polyneuropathies* (p 1499), *arthropathies*, certain of the *dermatoses* (p 3342) and *bronchial asthma*.

Atopy from Physical Agents.—*Heat*, *cold*, *light*, *solar energy* and *mechanical irritations* may produce typical allergic responses in sensitized end organs. The clinical reactions noted directly at the site of exposure include *swelling*, *urticaria*, *exudation* and *itching*; distant reactions include *vasomotor rhinitis*, *bronchospasm*, *generalized urticaria* or a *remote angioneurotic edema*.

Atopy of Psychogenic Origin.—Many clinical observations point to a close relationship between human atopy, autonomic imbalance (p 1595)

SECTION IV

NEOPLASMS

testinal cramps mucous colitis pruritus ani migraine epilepsy Menieres syndrome vertigo transitory attacks of aphasia and hemiplegia or angiospasms

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Atopy of Psychogenic Origin —Many clinical observations point to a close relationship between human atopy autonomic imbalance (p 1395)

CHAPTER 23

NEOPLASMS

The neoplasm is a structure which resembles but is not identical with the normal tissue in which it is located It grows without regard to the laws which govern and restrain the growth of normal tissue It is supplied with blood vessels and a sufficient supporting framework by the host from the latter it derives nourishment in exchange for which it contributes little or nothing that is useful and much that is potentially dangerous or lethal

BENIGN NEOPLASMS

Benign tumors are of epithelial endothelial or connective tissue origin They may be found anywhere throughout the tissues of the body

Clinical Manifestations—The benign tumor is recognized as an *innocent lump* It is usually sharply demarcated and rounded it may be minute or *enormous in size* *The uncomplicated benign tumor produces no subjective* symptoms other than swelling

Complications—The secondary results of benign tumor growths include manifestations that are cosmetic compressive functional vascular neuro logic and psychogenic

Skin neoplasms are often considered *cosmetic blemishes* benign brain tumors may produce *pressure symptoms cranial neuralgias* (p 1480) or *increase in intracranial pressure* (p 1421) compression of a peripheral nerve may result in a *mononeuropathy* (p 1489) or the pain that accom panies a *glomus tumor* (p 1435)

Adenomas of the pancreas are capable of resulting in attacks of hypo glycemia from *hyperinsulinism* (p 1242) Disturbances of growth may be attributed to hypersecretory activities in an *adenoma of the anterior pitui tary gland* (p 1155) many clinicians recognize the syndrome of *toxic adenomatosis of the thyroid* (p 1198)

The patient with benign tumor may suffer from *vascular disturbances* Anemic infarction may result in tissue degeneration in a *uterine fibroid* (p 2554) the increased vascularity of the *thyroid cystadenoma* (p 1222) produces a local bruit and thrill ulceration and hemorrhage may occur in submucous *uterine fibroids* and the *thyroid apoplexy* is followed by acute pain and swelling in a long standing gland cyst

The sudden twist of a *pedunculated ovarian cyst* (p 2564) produces the manifestations of an acute surgical emergency referable to the abdomen (p 1888) Simple cysts and swellings particularly of the female breast (p 2579) are often associated with intense *anxiety* and a *cancerophobia* The latter may be so severe as to constitute an indication for operative *surgery*

Diagnosis—The benign tumor requires differentiation from malignancy The *clinical features* which speak for the *innocence* of the growth include a history of long duration sharply defined encapsulation lack of evidence

COMPLICATIONS

Long continued allergy may produce *somatization* contactual sensitivities are invariably associated with a certain amount of *dermatitis* (eczema) protracted vasomotor rhinitis results in bacterial invasion and a secondary *bacterial allergy* (p 552) bronchial asthma sooner or later is associated with chronic bronchitis and *emphysema* (p 2056) There is some evidence to sustain the view that other end results of allergy include *periarteritis nodosa* (p 1027) *thrombo angiitis obliterans* (p 1029) *atrophic arthritis* and *eosinophilic pneumonitis* (p 2104)

DIAGNOSIS

The diagnosis of allergy rests upon the history demonstrations of sensitivity in the skin and mucous membranes the effects of elimination diets and the results of therapeutic trials



Fig 93 —Ophthalmic test Positive reaction in right eye

HISTORY

The diagnosis of an allergy is suggested by the history of the patient There are often *familial sensitizations* manifested by asthma hay fever or eczema The *past history* frequently suggests other allergic phenomena such as infantile eczema cyclic vomiting frequent colds dermatoses such as urticaria unusual responses to vaccination serum sickness severe reactions to immunizations for typhoid scarlet fever or diphtheria and unusual responses to drugs or foods

The *current history* of allergic complaints is often characterized by the dramatic onset of symptoms after contact with the offending substance which causes a rash symptoms of nasal or bronchial irritation digestive disturbances ophthalmic distress or an angiospasm Similar attacks of an exact nature may be recalled under similar circumstances these direct the suspicion of the patient to the offending agent

PHYSICAL EXAMINATION

In the interval between the attacks the patient may be symptom free and appears normal on examinations During the attack there are charac

THE PRECANCEROSES

The precanceroses are potentially malignant conditions which *may* be dermal or more deeply situated

The Precancerous Dermatoses—The precancerous dermatoses are elsewhere described in detail (p 3209) They may be (1) *benign growths*

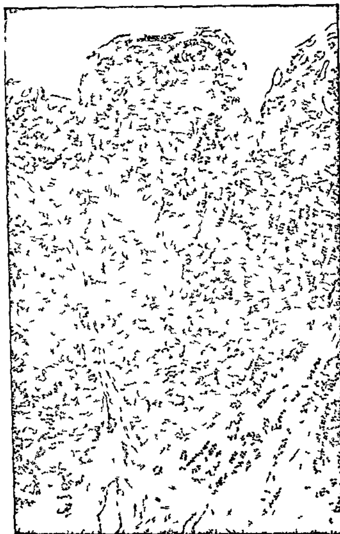


Fig 98—Papillomatous tumor of bladder showing invasive growth of some strands of epithelial cells

which assume the properties of invasiveness (2) malignant lesions arising in dermatoses caused by chronic irritation or infection or they may be (3) cutaneous lesions associated with *gonadal decrescence* The last include *senile keratoses* and *kraurosis vulvae*

test (4) the *intradermal* test and (5) the *passive transfer* technic of Prausnitz Kustner

Contact or Patch Test

The contact or patch test is employed for the detection of skin sensitivity to allergens

Technic—An oily or resinous substance or a dry powder may be applied directly to a small area of untraumatized skin Alcoholic or other solutions are applied to the skin on bits of blotting paper In any instance the test substance is covered with a square of cellophane or waxed paper and then fixed to the skin by a larger square of adhesive plaster A control with blotting paper cellophane or waxed paper and adhesive plaster should be made simultaneously The patch is observed at the end of twenty four and forty eight hours The patient should be instructed to remove the patch if undue itching or irritation occurs

A few simple *precautions* obviate most of the dangers of patch testing Testing should be avoided in the presence of an acute dermatitis As few substances as possible should be employed and the testing materials should be diluted and used in minute amounts The site selected for testing should be remote from the area of dermatitis and preferably in a cosmetically unobjectionable location The patient should be cautioned to remove the patch and cleanse the area if severe symptoms intervene

Complications and Their Prevention—A certain amount of danger is inherent in patch testing It is best not to perform patch tests except for a definite indication such as the necessity for discovering and making certain of the causal agents or for medicolegal testimony The untoward effects of patch tests may be local or general Local changes include excessive reaction with necrosis and ulceration followed by permanent scarring The general reaction usually is a widespread dissemination of the dermatitis which may lead to a prolonged illness

Patch Tuberculin Test

For the patch tuberculin test (Vollmer) it is only necessary to affix the prepared adhesive strip which contains gauze impregnated with the specific allergen (tuberculin) The interscapular region is a convenient site for the test since here the skin is almost invariably clear The standard test consists of 0 1 cc first strength Purified Protein Derivative (P P D) corresponding to 0 1 cc of standard Old Tuberculin 1 10 000 In the tuberculin patch test the patch is removed after forty eight hours and read after ninety six hours and at the end of another week A *positive reaction* is indicated by redness and swelling at the site of contact between patch and skin More intense reactions include vesiculation necrosis and gangrene

Ophthalmic Test

The ophthalmic test is used almost exclusively for the determination of *sensitivity to horse serum* Many of the therapeutic sera are packaged with an ophthalmic testing set The *technic* is exceedingly simple A drop of the diluted serum is instilled into the conjunctival sac Within from two to fifteen minutes there will in the sensitive individual be local congestion

more modern support for the importance of *parasitic invasion* has arisen from the experiments of Rous who has isolated a filtrable substance capable of causing sarcoma in the chicken on inoculation Shope has demonstrated the presence of a specific virus possessing the *power to originate* cutaneous papillomas

The importance of *cutaneous irritants* emanated from the work of Yamagiwa on tar cancer These animal experiments produced lesions resembling the malignancies observed in *chimney sweeps* (p 2440) The *organicists* (Cohnheim) give credence to the idea that the malignancy represented growth in a cell rest or inclusion of congenital origin The student of *parthogenesis* (Loeb) suggest fertilization of certain individual cytologic entities Students of chemistry (Warburg) point to *altered metabolic activity in cancer cells* which show a greater power of glycolysis an increased liberation of lactic acid and an abnormal growth stimulus Biologists (Murphy) have been impressed with the possibility that there is a loss of a *growth inhibiting factor* Geneticists point to a demonstrable *hereditary influence in animal experimentation and this is corroborated by* clinicians who observe cancer families

Precipitating Causes—*Clinical observations indicate that a malignant* lesion has a *quiescent* and an *invasive phase* The lesion exists as a potential *menace for variable periods before it assumes the characteristics of* lethality No one who has observed the sequence of events can doubt that some precipitating factor has transformed the potentiality into ominous actuality

CARCINOGENS—*In the discussion of the precanceroses reference was* made to a variety of miscellaneous carcinogenic conditions such as *mechanical trauma* the *chronic irritation* resulting from infection and exposure to solar and radiant energy the effects of *chemicals* such as tar soot aniline and a *miscellaneous group characterized by their possession of a phenanthrene ring nucleus*

In clinical practice the most disturbing of the carcinogenic substances are the *gonadal derivatives* In the experimental animal injections and inunctions *of estrogen are capable of producing mammary cancer clinically* the metastases from breast cancers seem to grow less rapidly following the production of an *artificial menopause* and the administration of *androgen* In the male *castration* seems to exert a favorable effect on prostatic cancer and its *metastases* (p 2450) *these benefits may be augmented when estrogens* are administered

In the present state of knowledge it is very difficult for the practitioner to steer a clear course relative to hormonal therapy The experimental and clinical evidences of carcinogenesis cannot be lightly *dismissed* On the other hand daily experiences attest the statistical safety of the administration of estrogen and androgen Our present attitude is that of *erring on the side of conservatism* We believe that the slightest hazard of inducing malignancy is excessive when human life is at stake *Except for* extraordinary circumstances we make every effort to omit administrations of estrogen to the female and androgen to the male In the presence of *precanceroses or a family history of malignancy* our contraindication are absolute

Clinical Manifestations—The practitioner should set himself the task

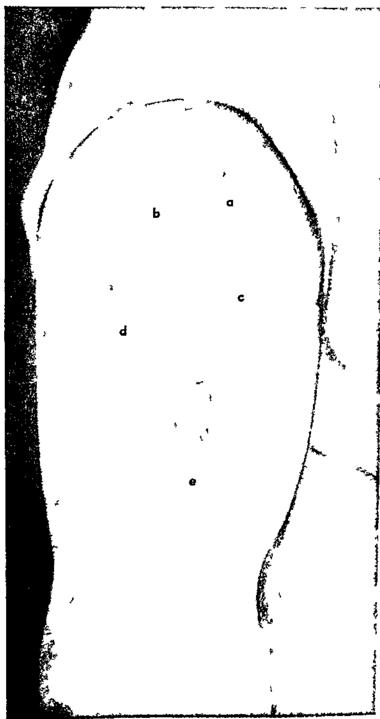


Fig 95 —Intradermal test Skin reactions after intracutaneous injection of allergenic extracts *A* Negative (control) *B* Doubtful *C* Slight *D* Moderate *E* Marked

Tuft Clinical Allergy

plasm rests upon its power of infiltration absence of capsular definition progressive growth the tendencies to ulcerate bleed and recur after local removal and the production of distant metastases

Biopsy Puncture and Aspiration—The practitioner who makes it a point of professional pride to recognize the malignancy in its potential phase leans heavily upon *tissue excision* and *histologic examination* Ewing has said the resort to biopsy is a confession of failure With this attitude

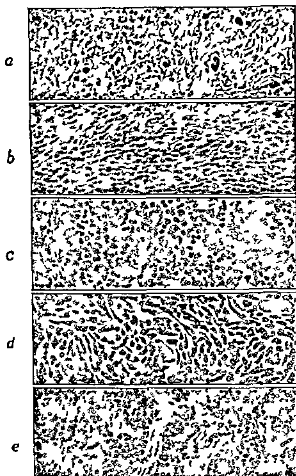


Fig 99—Several types of sarcoma *A* Mixed-cell sarcoma *B* Coarse spindle-cell sarcoma *C* Metastatic round-cell sarcoma *D* Sarcoma of thyroid with giant-cells *E* Sarcoma of ovary

we in all humility are in complete disagreement In potential malignancy of the skin bone jaw parotid neck cervix prostate accessible mucous membrane the pleura or peritoneum the rectum anus breast and testes we favor biopsy by puncture aspiration or local excision Whenever possible it is our practice to request the *pathologist* to be present when the specimen is obtained since he is best qualified to indicate the site for

MacCallum Textbook of Pathology

ing for sensitization Epinephrine should always be available for hypodermic use in the event of an untoward reaction In the presence of a positive ophthalmic test serum should be avoided or given in very small gradually increasing doses for desensitization (p 87) See *Serum Reactions* (p 85)

Drugs —Sensitivity to drugs can be tested by the patch method The method is unreliable for drugs absorbed from the gastro intestinal tract but of great value in the detection of sensitivity to locally applied sub stances, including *cosmetics* (p 3138)

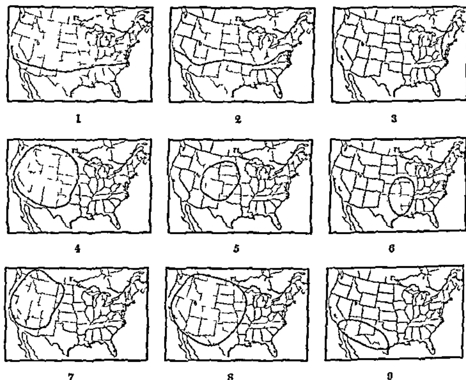


Fig 96 —Geographical distribution of various hay fever grasses and weeds The bound ary lines shown are only approximate It is impossible to show exact areas of distribution as the presence of a few specimens is not sufficient to cause hay fever symptoms Outside the shaded areas the plants are of minor or no importance in allergy *1* Blue grass and timothy *2* Bermuda grass *3* Sweet vernal grass *4* Russian thistle *5* Kochia *6* Western water hemp *7* Sagebrush *8* Prairie sage *9* Palmer s amaranth *

Contact Allergies —Contact allergies are probably of greater frequency than generally suspected They are being discovered in increasing numbers as the frequency of testing increases The test is performed by applying the offending substance directly to the skin according to the patch method (p 555) See *Contact Dermatitis* (p 3330)

Bacterial Allergies.—Antibodies to bacteria and bacterial products are demonstrable in immunity and are assumed to be provocative as well in bacterial allergy

* Reproduced with permission from the chapter on Pollens and Hay Fever by O C Durham in "Allergy in General Practice, by Samuel M Feinberg Lea and ulishers

TREATMENT

The phases of therapy in the problem of carcinoma include prophylaxis attempts at radical cure and the management of inoperability

Prophylaxis—The practitioner is the greatest single factor in the campaign against the ravages of cancer His efforts are directed at removal or destruction of precanceroses (p 571) the avoidance of exposure to carcinogenic agencies (p 573) and the excision of the malignant lesion in it potential phase before complications have developed

Radical Cure—Radical cure of the malignant lesion is attempted by radiotherapy surgical excision and electrocoagulation

Radiotherapy—Roentgen therapy alone is the method of choice in the management of radiosensitive neoplasms (p 3797) situated in accessible structures *implants of radium* are used in the body cavities

Surgery and Electrocoagulation—Successful surgical excision is dependent upon limited local manifestations absence of metastases and the nonvital nature of the tumor site The skilled technical surgeon is capable of removing without sacrifice of life as much as an entire lung the greater part of the stomach several feet of large intestine the uterus ovaries and tubes portions of the bladder a kidney the testes the prostate gland the larynx the tongue the esophagus and portions of the pancreas *Electrocoagulation* (p 2601) may have advantages over scalpel excision in that the vascular channels are sealed off at the time of destruction of the neoplasm

Combined Therapy—The combination of surgery and radiotherapy enhances the outlook for cure *Preoperative radiotherapy* at a small sacrifice of time may increase operability *Postoperative radiotherapy* directed at the operative site and the most common areas for metastases provides the patient with his optimum chance The procedures of choice for each neoplasm are separately discussed in the chapters dealing with neoplasms of the various body systems

The Management of Inoperability—The greatest human trial to patient and practitioner is that of dealing with the problem of inoperable malignancy The clinician is armed for this unequal conflict with physical biological palliative and psychotherapeutic agencies

Roentgenotherapy—The inoperable lesion may be attacked by roentgenotherapy and radium implants The exponents of these modalities claim to control radiosensitive growths (p 3797) but our experiences have been sad and discouraging although we have no more efficacious agency to suggest

Biological Therapy—Malignancies of the *female breast and reproductive organs* may be treated by roentgen or surgical castration and androgen *Prostatic malignancies* in similar fashion are exposed to roentgen or surgical castration and administration of estrogen (p 2515)

Palliative Treatment—The palliative treatment of malignancy is directed primarily at the control of pain An attempt is made to withhold the opiates for the final stages *Localized pain* is relieved whenever possible by alcohol injections and infiltrations paravertebral injections sympathectomy chordotomy neurectomy implantations of radium and intensive roentgentherapy

Sooner or later when the pain becomes uncontrollable and more widely

ELIMINATION DIETS

Indications—In the presence of suspected *food allergy* where the history is not clearcut various foods may be eliminated one at a time by a series of elimination diets devised by Rowe

It is clear that certain of these diets are deficient in vitamins For example Diet IV contains only milk and the other diets exclude milk For safety's sake it is wise to administer vitamin concentrates as supplements to the diet and where milk has been omitted to give tablets of calcium gluconate

Technic—The patient is placed on one or the other of these dietary regimes for a period ranging from ten days to three or four weeks During that time he must adhere strictly to the diet and take no other food whatsoever It is advisable for him not to eat in a restaurant where the ingredients of his food can never be completely known to him

Type Diets

DIET I

(No milk rye beef pork, poultry corn)

Rice tapioca rice biscuit, rice bread
Lettuce spinach carrots beets artichokes
Lamb
Lemon grapefruit, pears
Cane sugar
Wesson oil olive oil salt
Gelatin syrup made of maple sugar or cane sugar flavored with Mapleine or maple sugar
Olives
Peanut butter

DIET II

(No lamb beef rice milk)

Corn rye corn pone corn rye muffins rye bread rye crisp
Tomato squash asparagus peas string beans
Chicken bacon
Pineapple peaches apricots prunes
Cane sugar
Mazola oil Wesson oil salt
Karo corn syrup
Gelatin

DIET III

(No rice lamb poultry milk rye)

Tapioca
White and sweet potato lima bean potato bread soy bean lima bean bread
Beets carrots lima beans string beans tomato
Bacon beef
Lemon grapefruit, peaches apricots
Cane sugar
Olive oil Wesson oil gelatin salt
Olives
Maple syrup *or syrup* made with *cane sugar flavored with maple*

DIET IV

Milk up to two or three quarts a day
Tapioca, cooked with milk and milk sugar may also be taken

SECTION V

METABOLISM

Associate Editor CLIFFORD R SPINGARN M D

to seven day intervals When pollination occurs the maximum dose is reduced to approximately half if the course of therapy has not been completed If the patient has been negligent and has not reported for treatment until a few weeks prior to pollination daily doses may be attempted provided there are no severe reactions

In *coseasonal immunization* the initial dose is chosen as indicated above This initial dose is given daily for three doses and is then increased by 0 1 cc at daily intervals provided there is no severe reaction

The *perennial plan* of treatment accomplishes full immunization and then repeats the maximum dose at weekly fortnightly or monthly intervals until the approach of pollination At this time the intervals are shortened and an attempt is made to maintain the immunity without interruption

Reference has been made elsewhere to the management of treatment failures in pollen desensitizations (p 2097)

Anti histamines—Recognition of the essential role of histamine in the production of the syndromes of allergy has led to many attempts to transmute knowledge into terms of practical therapy Desensitization to histamine despite initial favorable reports has proven disappointing as have attempts to stimulate histamine antibodies by injections of histamine conjugates such as histamine azoprotein Efforts to introduce histaminase (Torantil) an enzyme capable of destroying histamine were equally unconvincing

In 1937 efforts were directed towards the synthesis of anti histamine agents These have met with remarkable success through the discovery of Antergan and Neo Antergan in France and of benadryl and pyribenzamine in America

Benadryl (beta dimethylamino ethyl benzohydryl ether hydro-chloride) is marketed in capsules each containing 50 mg *Pyribenzamine* (N1 pyridil N1 benzyl N dimethyl ethylene diamine) is available in tablets also of 50 mg strength Either preparation may be taken in a dose of 50 to 100 mg four times daily affording phenomenal symptomatic relief in the majority of patients suffering from whealing angioneurotic edema (p 3349) urticaria (p 3345) acute and chronic atopic dermatitis (p 3342) contact dermatitis (p 3330) serum sickness (p 548) migraine (p 1506) pruritus ani and vulvae erythema multiforme (p 3377) vasomotor rhinitis both seasonal hay fever (p 2097) and non seasonal hay fever (p 2098) asthma (p 2101) Meniere's disease (p 1486) penicillin reactions and all other clinical allergies Antispasmodic effects are noted in dysmenorrhea cardiospasm pylorospasm and vesical spasm Gastric relief is enhanced by additional suppression of acid secretion

Untoward reactions are encountered with both preparations These include drowsiness ataxia dizziness dryness of the mouth nausea dysuria and headache They are less frequently encountered with pyribenzamine than with benadryl Pyribenzamine has the further advantage over benadryl in that it exhibits slightly greater efficacy and hence is to be preferred reserving benadryl as a second choice if the allergic symptoms are resistant or the patient complains of side effects

Symptomatic Therapy.—Symptomatic treatment of the allergic states consists in adequate *rest* and *sleep* *free catharsis* and the adherence to the general rules of *physical and mental hygiene* (p 1316) During the periods

CHAPTER 29

AN INTRODUCTION TO THE STUDY OF METABOLISM AND NUTRITION

METABOLISM is the study of the aggregate of the chemical reactions that take place in the living organism The processes of metabolism may be catabolic or anabolic In *catabolic reactions* materials are broken down into their simplest components in order to furnish energy heat or the elements for tissue growth and tissue repair in *anabolic phenomena* substances are built and incorporated into the more complex body framework

Metabolic processes may be *calorigenic* or *noncalorigenic* The former produce results that are measurable in terms of energy (calories) the calorigenic foods are *carbohydrates fats* and *proteins* Noncalorigenic metabolism is of equally great significance though it cannot be measured in terms of energy the noncalorigenic factors in metabolism are the *minerals* and *vitamins*

Exogenous and Endogenous Metabolic Disorders—The metabolic disorders are of great variety and complexity Many are *exogenous* and are related to food intake food preparation and the absorption assimilation and excretion of the metabolic products others are *endogenous* and bear little relationship to the diet The latter include many of the endocrinopathies such as diabetes mellitus

The Prevalence of Exogenous Nutritional Disorders—Recent estimate in our great nation of plenty indicate that more than a third of our population is malnourished or suffering from the effects of dietary imbalance Some of this is ascribable to poverty but most is the result of ignorance and carelessness

The Scope of Metabolic and Nutritional Disorders—The scope of metabolic and nutritional disorders is best attested by the following list of integrations Some of these conditions such as *albuminuria* are symptomatic others like *diabetes mellitus* are endocrinopathies Many like the *lipomatoses* are mysterious afflictions whereas the *avitaminoses* are clearly recognizable and remediable

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Scope of Present Section —In the present section an attempt has been made to coordinate the essential principles of metabolism and nutrition with the practical details of differential diagnosis and therapeutics The essential constituents of the American diet and the methods of preparing and preserving food are discussed in Chapter 30 Practical dietotherapy in health and disease constitutes the subject matter of Chapter 31 and the section is concluded (Chapter 32) with the Differential Diagnosis and Management of the Commoner Disorders of Metabolism

time and with extraordinary efficiency whether or not the driver stops to refuel when the tank empties

NORMAL ENERGY REQUIREMENTS

Basal Needs.—Normal individuals at complete rest and in the post absorptive state expend a fairly constant amount of energy which is designated as the *basal metabolism* The rate is determined largely by cardiorespiratory movements and the maintenance of muscle tone The actual basal metabolism varies with the age sex weight and height of the individual and is normally in the vicinity of 40 calories per square meter of *body surface per hour* or about 1700 calories per day The technic of basal metabolism determinations has been described (p 3738) The various factors that modify the basal metabolism are discussed elsewhere (p 716)

Work Needs—*In addition to basal metabolism the energy expenditure of the body is dependent upon muscular activity A manual laborer* uses up more energy than a sedentary worker A tailor or a bookbinder who sits all day at his work requires from 700 to 800 calories above the basal A carpenter lumberjack or soldier may need an additional 3000 to 4000 calories to meet the needs of muscular activity

Other Needs.—Other factors that contribute to the total energy expenditure are the specific dynamic action of the foodstuffs the energy expended in the digestion and absorption of food the effects of climate and growth In cold regions more energy must be converted into heat to maintain the body at a constant temperature hence more food is required Growing children require 70 to 100 per cent more calories than the basal requirements The pregnant or lactating woman also has an increased nutritional requirement

METABOLISM OF WATER

Water *constitutes approximately* three quarters of the weight of the human body *This solvent is the greatest common divisor of life* Unless fluid requirements *are maintained life cannot* endure *beyond a period of a few days in contrast to the relatively long periods of survival during* food deprivation

Water Intake—Body water is *steadily* replenished by *preformed water* obtained from the ingestion of liquids and of foods with a high moisture content *Water of oxidation* is liberated during metabolism 100 grams each of fat carbohydrate and protein *yield* respectively 107 55 and 41 grams of water The burning of 100 grams of alcohol causes the formation of 117 grams of water

Absorption of Water.—*Preformed water* is absorbed from the upper small intestine within 15 to 30 minutes after ingestion Anesthetics narcotics and similar substances slow the alimentary absorption of water by hindering its passage through the stomach

In addition to ingested water three to four liters of salivary gastric and intestinal secretions enter the bowel Despite this increment water absorption is so successful that only 300 cc of the total of ingested and secreted fluids reach the ileocecal valve The unabsorbed water present in the stool moistens the fecal residue and assists defecation

Water Output.—Water is excreted by kidneys skin lungs and intestinal

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of growth and absence of any tendency to infiltration, ulceration, hemorrhage or metastasis

Growths of recent origin which increase in size and tend to ulcerate or bleed require *biopsy* or *total extirpation* Sections are examined by the *tissue pathologist* who searches for the histological features of malignancy (p 3753)

Treatment—The treatment of the benign neoplasm most often invokes the principle of *skilful neglect* (p 3753) The patient is urged to return

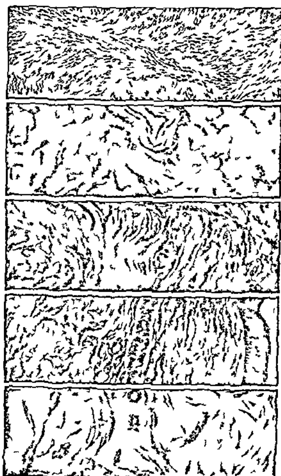


Fig 97—Types of fibroma

for examination upon the appearance of any of the clinical features of malignancy (p 573)

If it becomes necessary to extirpate the growth we prefer *surgical removal* and *histologic examination* Destruction by chemicals or by roentgen therapy deprives the physician of his most valuable information It is far better to perform a hundred useless microscopic surveys than to omit one that might provide information of value in the early *diagnosis* of malignancy

* MacCallum Textbook of Pathology

body temperature Effective antipyretic measures include the sponge bath and the cold pack

Digestive Effects—The ingestion of water with meals has a decidedly beneficial effect upon the digestive organs Water aids the action of saliva and improves mouth hygiene It favors a copious flow of gastric and pan creatic juice An adequate fluid intake prevents stasis and inspissation of the stool it decreases the amount of bacterial putrefaction in the large intestine and favors free elimination The therapy of chronic constipation should include a liberal consumption of water (1600 to 2000 cc daily)

Maintenance of Hydration—The forcing of fluids (3000 to 5000 cc daily) is of great value to the febrile patient A liberal water intake prevents dehydration from sweating and maintains a copious elimination of dilute urine which assists in the excretion of toxins The end results are greater comfort for the patient and well hydrated tissues whose defensive and recuperative powers are free from the burden of dehydration

The forcing of fluid by the oral route is usually accomplished by giving sweetened tea fruit juices and chilled water carbonated or flat

As a Diuretic—Water is an excellent diuretic and aids in the excretion of metabolites and drugs Its diuretic action depends upon the salt content of the extracellular fluid and the functional state of the adrenal cortex and posterior pituitary In patients with impaired renal function a polyuria resulting from free water drinking often maintains renal compensation

As a Protective—A dilute urine minimizes renal irritation from nephro toxic drugs It prevents the precipitation of crystals and calculi derived from metabolic salts (uric acid phosphate oxalate) or drugs (sulfathia zole)

Parenteral Administration—Water is supplied by subcutaneous or in travenous routes when enteral administration is contraindicated because of vomiting and diarrhea Commonly water is given as physiological saline solution In the intravenous drip which furnishes 3000 to 4000 cc daily the salt content is excessive (27 to 36 gm daily) It is good clinical prac tice to follow the first liter of physiological saline solution with succeeding liters of distilled water for the remainder of the twenty four hours In con ditions of acidosis sodium r lactate solution is preferable because of its excess of sodium ion Dextrose solutions have a tendency to dehydrate and should be avoided in conditions characterized by a negative water balance

Dangers of Water Administration—Water is often productive of delete rious effects in cases of *heart disease* Failure to restrict fluid favors cardiac decompensation The retention of fluid in the tissues is increased unless water intake is curtailed The consumption of large amounts of water after profuse sweating leads to muscle cramps This can be prevented by simul taneously replacing the salt which is also lost

Heavy Water or Deuterium Oxide—Heavy water or deuterium oxide is of considerable pharmacological interest but has no therapeutic utility at the present time

METABOLISM OF CARBOHYDRATES

Carbohydrate is the chief source of the energy required for muscle activity and heat production It furnishes more than half of the calories

The Deeper Precanceroses—Precanceroses also are noted beneath the skin They may be observed in the female *nipple* and *breast* (p 2581) the *cervix of the uterus* (p 2551) the *urinary bladder* the *rectum and anus* (p 1917), in *polyps of the large bowel* (p 1865), and in *ulcers of the tongue* (p 1689) We are not among those who regard the peptic ulcer (p 1783) as a precancerous condition We have never observed the described malignant degeneration of *chronic infectious granulomas* such as are reported to occur in syphilis tuberculosis and Hodgkin s disease Those familiar with *bilharziasis* (p 2341) testify to the frequent association of bladder infestations and malignancy

Clinical Manifestations—The possibility of malignant degeneration in a precancerous lesion is suspected when the structure *increases in s e in filtrates ulcerates* or *hemorrhages* The suspicion becomes stronger if there is *recurrence* after removal of a localized lymphadenopathy The appearance of any one of these factors is sufficient indication for immediate histologic examination complete excision of the area and its satellite glands and prophylactic radium or roentgen therapy (p 3793)

Treatment—Since it is obviously impossible to extirpate all precanceroses the physician's initial responsibility is to prevent malignant change The patient is ordered to refrain from *traumatizing* a local lesion Those with *keratoses* (p 3215) are not given oral arsenicals and are forbidden to participate in occupations which involve the handling of *tar tar distillates pitch* or *soot* medical personnel exposed to *roentgen rays* are warned concerning the use of protective measures and great caution is exercised by the physician in the administration of carcinogens such as *estrogen* (p 2515) to women and *androgen* (p 2404) to men

Single lesions are removed *surgically* and examined *histologically* Multiple lesions require repeated examination since it is impractical to remove large numbers of moles nevi adenomas and fibromas When the decision for surgery has been reached complete and wide excision is advisable with histologic examinations of the deeper tissues and the edges If there is any suspicion of malignant change the area of the scar and the satellite lymph nodes are given prophylactic roentgen therapy The patient is ordered to report any later recurrent infiltration or growth

MALIGNANT NEOPLASMS

The malignant tumors include *sarcomas* and *carcinomas* The problem of dealing with these insidious and lethal conditions constitutes one of the most important challenges in modern medical practice

Etiology—The etiology of malignancy is at present unknown The majority of investigators do not regard malignancy as a single disease condition but as an *abnormal tissue response* probably dependent upon the operation of many diverse factors The salient characteristics of the cancer seem to be its failure to obey the laws of normal growth a sudden and profound change in the character of the cells a loss of growth restraint purposeless lawless never ending cell division and the assumption of reproduction without function"

Many theories have been offered as having possible bearing on these lethal changes The earliest experimental data were obtained through the production of malignancy by *Spiroptera* a nematode worm (Fibiger) The

Absorption of Carbohydrate—*Dextrose* is readily absorbed into the circulation without any alteration in the molecule *Fructose* undergoes partial conversion into dextrose in the intestinal mucosa the remainder being completely converted in the liver *Galactose* is converted to dextrose in the liver The ability of the liver to remove ingested galactose from the circulation is the basis of a sensitive liver function test See *Galactose Tolerance Test* (p 1949)

The disaccharides may escape conversion in the upper intestinal tract and reach the large intestine In the case of lactose this phenomenon is employed therapeutically in order to alter the bacterial flora the acidophilic bacteria growing luxuriantly in the presence of lactose Under these circumstances the gram negative colon group fails to thrive and the bacterial flora is converted to one that is predominantly gram positive

Occasionally in normal people small amounts of other monosaccharides (pentoses) are absorbed This usually occurs after the ingestion of large quantities of fruit These sugars are not metabolizable and are rapidly excreted in the urine See *Pentosuria* (p 3077)

Utilization of Available Carbohydrate—After absorption and passage to the liver part of the available carbohydrate is stored as liver glycogen part as muscle glycogen and part as fat Some is oxidized depending on the energy requirement Available carbohydrate circulates as dextrose the form in which it is utilized

The carbohydrate of the diet is not the only source of dextrose One hundred grams of protein yields 58 gm of dextrose due to its content of sugar forming amino acids Additional amounts of dextrose are formed from glycerol lactic acid and pyruvic acid

Factors Influencing Metabolism of Carbohydrate—The proper utilization of carbohydrate depends upon the normal interaction of several factors which maintain an equilibrium between the absorption storage and oxidation of dextrose These include (*a*) the integrity of intestinal digestive and absorptive mechanisms (*b*) the functional activity of the liver which stores glucose as glycogen (*glycogenesis*) and forms it from glycogen (*glycogenolysis*) and protein (*glucogenesis*) (*c*) the status of endocrine function especially with regard to insulin (p 1237) (*d*) the oxidation of glucose by the various tissues especially the muscles

The nicety of the interplay of these mechanisms is reflected in the constancy of the blood sugar level When a large amount of glucose is oxidized and the concentration in the body fluid tends to fall more is liberated from the storage depots and if necessary from protein breakdown If the supply exceeds the peripheral oxidation the excess is stored as glycogen and fat If the blood sugar concentration rises some is excreted in the urine Disturbances in the equilibrium between absorption storage and utilization are reflected in changes in the blood sugar level See *Hyperglycemia* (p 733) *Hypoglycemia* (p 734)

Effect of Glucose on Insulin Production—The effect of glucose on insulin production is of importance in understanding certain types of *obesity* (p 698) as well as the *hypoglycemic reactions* (p 733)

The secretion of insulin is stimulated by elevation of the blood sugar Once stimulated insulin may be secreted to excess This may produce a precipitate fall in the blood sugar level The individual may react in one

of diagnosing malignancy in its potential phase when the only clinical finding is the presence of a lump Other phenomena related to the cancer constitute complications the presence of any of which jeopardizes the chance for total extirpation and cure'

The manifestations which lead the physician to suspect malignancy in a *precancerosis* are elsewhere discussed (p 572) The diagnosis of primary cancer before the onset of complications requires a high *index of suspicion* on the part of the examiner a knowledge of the common sites where growths occur and the willingness and humility to make meticulous and repeated examinations

The routine physical examination includes a survey of the skin the oral mucous membranes and the tongue The *prophylaxis* of malignancy demands inspection palpation and transillumination of the female mammary glands (p 3632) Frequent rectal and vaginal palpations disclose the asymptomatic phases of malignancies of the *rectum anus vagina ovary uterus testes* and *prostate gland* The persistence of painless urinary bleeding is an absolute indication for investigation of the lower and upper urinary tract by *cystoscopy* (p 2248) and *intravenous pyelography* The middle aged patient who suddenly becomes hoarse requires *laryngoscopy* (p 2024) by the expert With persistent digestive symptoms in the upper or lower tract a visual instrumental survey is required followed by x rays and frequent examinations of the *stools* for evidence of bleeding (p 3728) Intractable bone pain with or without the presence of pathological fractures suggests the need for *roentgen study* and *specialist consultation*

Complications —The complications of carcinomatosis are local and distant Infiltrations are observed in *mammary cancer* with demonstrable lymphadenopathy in the axillary region the *ovarian lesion* tends to become implanted on the peritoneal surfaces and produce an *ascites gastric cancers* may ulcerate or hemorrhage the presence of a *pulmonary new growth* may be heralded by a painless hemoptysis and the *bladder carcinoma* often starts with the passage of bloody urine Malignant lesions of the *large bowel* tend to produce obstruction but they may penetrate and perforate with initial manifestations of an acute or subacute peritonitis (p 1923)

Distant complications whose presence excludes the hope of operative cure include *metastases* by extension embolism or through lymphogenous or hematogenous channels Equally ominous are the *systemic signs* which include loss of weight and strength anemia rapidity of the sedimentation rate of the erythrocytes leukocytosis and fever The last is often an *aseptic pyrexia* (p 23) as particularly illustrated in the *osteogenic sarcomas* (p 2843) The confusing *leukocytosis* may occur independently of infection and is probably a metabolic phenomenon Despite the enthusiasm of proponents estimation of the *sedimentation rate* in our experience is often misleading The fact that it is normal must not prevent the continuation of the search for a malignant focus nor lull the investigator into a sense of false security

One of the striking characteristics of the malignant lesion is the continuation of its increasing growth while the host becomes progressively cachectic Man s inhumanity to man is dwarfed by this caprice of nature

Diagnosis —The clinical diagnosis of the malignant character of a neo

in the treatment of epilepsy Meniere s disease and urinary tract infection In the first two instances the acidosis is used to produce *dehydration* in the latter to make the urine acid

THE SUGARS

Therapeutics —The oral administration of the sugars is advocated for purposes other than mere nutrition The ingestion of the simple sugars combats acidosis and hypoglycemia *Lactose dextri maltose* and the *starches* are employed in the milk formulas for infant feeding (p 2751)

Lactose and *beta lactose* are used in the treatment of *intestinal toxemia* in the adult The administration of these sugars favors the growth of the *Bacillus acidophilus* in the intestines The gram negative colon bacillus and the *Streptococcus faecalis* succumb to the richer growth of the gram positive acidophilus organism Many clinicians believe that this change in the flora effectively combats intestinal toxemia or auto intoxication

Parenterally the sugars are most easily administered intravenously For the continuous intravenous drip 2.5 to 10 per cent solution of dextrose *in distilled water or physiological saline solution* may be infused up to 3000 cc daily Commercially flasks containing 250 to 1000 cc may be purchased and stored

The more concentrated solutions of the sugars (50 per cent solution) are used (1) in the treatment of the *hypoglycemic* reaction (2) for the reduction of *increased intracranial pressure* due to tumor or hypertension and (3) in *pulmonary edema* and *myocarditis* Fifty per cent dextrose *solution is the most easily available However those who are* especially interested in the neurological disorders prefer 50 per cent *sucrose* solution or *sorbitol* The concentrated solutions are used in amounts varying from 50 to 100 cc

METABOLISM OF PROTEIN

Metabolic Role of Protein.—The protein of the diet supplies materials required (*a*) for the *growth* and *repair* of tissue (*b*) for the *formation of various secretions hormones enzymes* and *antibodies* and (*c*) *as a potential source of carbohydrates*

Structure of Proteins —The proteins are complex molecules composed of nitrogen containing amino acids The various proteins are distinguished by their content and arrangement of *amino acids* So far twenty two different amino acids have been isolated from plant and animal proteins

Certain simple amino acids (glycine alanine) can be synthesized in the body Others (tryptophane histidine phenylalanine leucine isoleucine thyronine methionine valine cystine) cannot be synthesized and must be supplied in the diet since they are essential for normal growth and health

The nutritional value of protein is dependent on the content of essential amino acids Proteins such as the lactalbumin of milk ovalbumin of eggs beef protein and glutenin of wheat contain all essential amino acids and are of the *greatest nutritional value It is important to realize* that the utilization of a protein deficient in certain amino acids is limited

The Normal Protein Requirement —The normal diet should contain about one gram of protein per kilogram of body weight In the average dietary this amounts to about 60 gm of protein and 15 per cent of the total

the biopsy and the amount of tissue required Serious errors may result from the examination of inadequate portions of the tumor and the appearance of sections that are badly cut

Endoscopy —The body activities are viewed and specimens are obtained by *uterine curettage esophagoscopy gastroscopy sigmoidoscopy cystoscopy laryngoscopy* and *bronchoscopy*

Exploratory Operations —For *deeper neoplasms* such as the palpable intra abdominal tumor we favor *performing* exploratory operation It is far better on several occasions to open an abdomen and happily report an error of commission than to view the tragedy of a single abdominal closure in which inoperability was the price of an error of omission or ultraconservatism Consistent with this policy we favor *diagnostic nephrotomy thoracotomy pneumonotomy craniotomy* and *laminectomy*

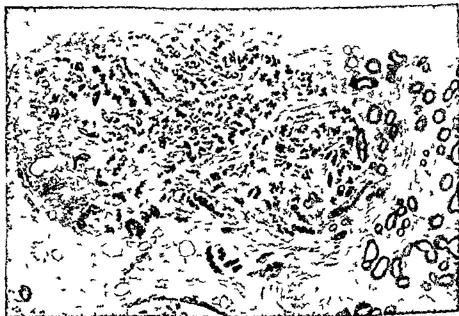


Fig 100 —Development of a carcinomatous nodule in an adenofibroma of the breast The invasive character of the carcinoma cells is apparent *

Radiosensitivity —The diagnosis of malignancy may be inferred as the result of roentgen therapy Radiosensitivity characterizes *lymphoid* and *myeloid tumors* rather than the chronic infectious granulomas of tuberculosis and syphilis

Histology —The cytologic features of malignancy are specialist province They include invasiveness lack of capsulation the presence of abundant mitoses anaplasia hyperchromia of the nucleus a coarse nuclear network varied nuclear shapes an eccentric nuclear position a nucleus that is large in relation to the nucleolus and a perinucleolar halo

The Grading of Malignancy —Attempts have been made to grade the malignancy according to the histologic appearances previously described Those in which there is the most malignant change are rated *IV and* are inoperable Lesions of grades I and II show only minor changes and are *as a rule* still amenable to surgical therapy

* MacCallum, Textbook of Pathology

cereals 20 per cent comes from milk and milk products Thus approximately half of the protein of the diet is derived from these sources Of the remaining 52 per cent approximately one half is of beef or pork origin the remainder from poultry eggs and corn

Purine Metabolism and Uric Acid—Uric acid is one of the end products of nucleoprotein metabolism Its metabolism in human beings is poorly understood and differs greatly from that of other animals Its major interest is its relation to gout and to uric acid stones

Nucleoproteins are present in all living nuclei Proteins derived from organ meat are especially rich in nucleoprotein while eggs which contain only one nucleus are particularly poor in nucleoprotein Milk and dairy products are also poor in this material

Caffeine and theobromine which are methylated purines are never transformed into uric acid in the human body

Chemistry of the Nucleoproteins and of Uric Acid—Uric acid xanthine and hypoxanthine are amino purines which are ring compounds containing nitrogen They are derived from the hydrolysis of nucleic acid which is one of the hydrolyzed products of nucleoprotein The other products of the hydrolysis of nucleic acid are sugar phosphoric acid and pyrimidines which form urea and have no relation to purine metabolism

Metabolism of Ingested Nucleoproteins—The protein component of nucleoprotein is split off from nucleic acid by the action of pepsin and trypsin in the stomach and small intestine The nucleic acid is successively hydrolyzed in the small intestine to form inosinic acid in which form it is absorbed by the liver where the breakdown to uric acid is completed Some of the products derived from nucleic acid escape absorption and are decomposed by the bacteria of the colon into ammonia

In most mammals other than the human and the ape uric acid is broken down by the enzyme uricase into allantoin

There is some evidence that purines are synthesized in the organism Humans on a purine free diet continue to excrete uric acid derived from endogenous nucleoprotein metabolism

Uric Acid Excretion—Uric acid is excreted predominantly in the urine The renal tubules have a very low concentrating power in human beings This accounts for the high serum uric acid level of humans which is 3 to 6 mg per 100 cc of blood Uric acid excretion is diminished under the influence of starvation a high fat diet exercise or the ingestion of lactic acid This is attributed to the resulting acidosis of these conditions

Certain drugs influence the elimination of uric acid Epinephrine increases the excretion of uric acid whereas pituitrin ergotamine and atropine have a depressing effect There is increased uric acid excretion in the pathologic states in which unusual amounts of nucleoprotein are destroyed such as leukemia and polycythemia

Therapeutics—*High protein diets* are employed in the states characterized by hypoproteinemia *Low protein diets* were formerly advocated in diseases of the excretory organs such as nephritis It has become increasingly evident however that protein deprivation in the diet is apt to cause protein loss from the endogenous sources and thus be a therapeutic boomerang (p 2282)

Predigested protein and *purified amino acids* are commercially available

spread the simpler *analgesics sedatives* and *hypnotics* are required Later it becomes necessary to augment those with demerol (p 3863) or the *opiates* (codeine dilaudid and morphine) The drugs are given orally later suppositories are tried and finally a member of the family is taught to give a hypodermic injection Extreme instances require intravenous medication by the physician The liberal use of *alcoholic beverages* is often a boon and provides drug synergism with the opiates

Crymotherapy (p 3785) —Refrigeration therapy, by the artificial production of hypothermia has been attempted in the effort to control the growth of the malignancy Despite high initial hopes the method has proved futile for these purposes

Psychotherapy —The physician requires the exercise of all of his skill fortitude and courage when he is burdened with the task of dealing with his patient friend who suffers from carcinomatosis It is our principle to lie and lie in an effort to prevent the patient from knowing the nature of his affliction The nearest of kin is acquainted with the situation and asked to assume part of the burden of the responsibility Those who worship at the shrine of absolute truth and the dwellers in the ivory towers may condemn this practice if they will We have never seen any human being made happy by the revelation that he or she was the victim of a hopelessly malignant condition but we do know that many persons have had days or weeks or months and even years of relative solace and some measure of peace and hope from the substitution of a white lie for a black truth

The physician who lies to his patient with inoperable carcinoma does not relieve his own burden From the moment that the untruth is uttered he is faced with increasingly difficult situations He must continue to visit his patient friend with faithfulness his attitude cannot be dour nor can it be suspiciously jovial he must find ingenious explanations for the persistence of symptoms and the development of fresh complications Successfully to carry out his machination he must have the patience of a saint the ingenuity of Baron Munchhausen the slyness of the artful dodger and the inventiveness of a wizard

An endeavor which combines analgesia and fortification of the lie involves the injection once twice or thrice daily of intravenous doses of a combination of *dilaudid 0 002 gm* (1/32 grain) and *hyoscine hydrobromide 0 0005 gm* (1/120 grain) These are given as serum injections in increasing doses to relieve pain and produce the amnesia of twilight sleep

Euthanasia —There is an increasing demand for the legalization of euthanasia Societies have been formed to further this plan which would permit committees of physicians lawyers ministers and laymen to sanction painless death for carcinomatous patients who desire the termination of their lives Despite the earnestness of the advocates for euthanasia we are not yet prepared to enter their ranks We have been impressed by the tenacity with which the hopelessly afflicted cling to the tenuous thread of life we are conscious of the possible abuses of the method by opportunistic and criminal elements and we pride ourselves on the fact that the outlined methods of therapy can provide priceless hours of life

within the body The phospholipids are involved in the transport in the body and intermediate metabolism of fatty acids

STEROLS —Cholesterol the best known sterol is a constituent of every cell It is chemically related to the bile acids the sex hormones (androgen estrogen and adrenal cortical extract) carcinogens and cardiac glucosides such as digitalis Whether cholesterol can be changed into these substances or whether it has any physiologic relationship to them has not been shown Cholesterol ester *is normally present only in the blood plasma and renal cortex but abnormally may occur in deposits in various parts of the body* such as fatty livers atherosclerotic arteries gallstones and xanthomatoses

Digestion and Absorption of Fats—The food fat contains a small per centage of free fatty acids (less than 10 per cent) In the stomach the amount of fatty acid is slightly increased by the enzymic action of the gastric lipase The presence of fat slows the gastric emptying time In the duodenum the free fatty acids are neutralized to form *soaps* by the alkali present in the bile and pancreatic juice These soaps divide the unsplit fat physically into finely divided globules (emulsification) which by increasing the surface of the fats increases the effectiveness of enzymic *hydrolysis by pancreatic lipase Chemical splitting or hydrolysis results in* the formation of *fatty acids* and *glycerol*

The fatty acids being insoluble in water combine with bile salts (sodium salts of glycocholic and taurocholic acids) to form soluble com plexes which are absorbed by the intestinal mucosa Within the mucosal cells the fatty acids are recombined into fine globules of neutral fat by means of the phospholipids of the intestinal epithelium They then enter the intestinal lymphatics (lacteals) and are carried via the thoracic duct to the blood stream After a meal (4 to 6 hours) the serum appears milky due to the large quantity of fine fat globules (chylomicrons) Some of the fatty acids are combined to form phospholipids (phosphorylation) and cholesterol es ers These enter both the portal and lymphatic systems

Upon entry into the blood much of the neutral fat is broken down in the liver and resynthesized into phospholipids and cholesterol esters These latter compounds serve as a mechanism for the transport of fatty acids to the tissues where they are stored or oxidized

The Role of the Liver in Fat Metabolism—The liver occupies an important place *in the intermediary metabolism of fat* It desaturates fatty acids and synthesizes phospholipids and cholesterol esters It also acts as a temporary storage place for fat absorbed from the intestine and is the principal site of ketone body formation

Choline and Fat Metabolism—Under normal circumstances the fat con tent of the liver remains remarkably constant However there are a num ber of conditions in which large accumulations of hepatic fat occur These include high fat low protein diets fasting after cholesterol feeding after injections of anterior pituitary extracts and in severe diabetes

Accumulation of liver fat may be prevented by oral administration of choline This substance is a normal constituent of the pancreas and may be the active factor in the various pancreatic extracts used in treatment of fatty infiltration of the liver such as lipocaic (see p 1237) Choline is found in brain egg yolk glandular products and meat It may also be synthesized by the body Its synthesis requires the amino acid methionine

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INTEGRATIONS FOR DISTURBANCES OF METABOLISM

Total Metabolism
- **Disturbances of Growth (p 691)**
- **Disturbances of Weight (p 694)**

Energy Metabolism
- **Disturbances of Oxygen Consumption (p 716)**
  - **Increased Basal Metabolic Rate (p 720)**
  - **Decreased Basal Metabolic Rate (p ,19)**

Disturbances of Body Fluids
- **Dehydration (p ~04)**
- **Hyperhydration (p 705)**
- **Decrease of Plasma Volume (p 706)**
- **Increase of Tissue Fluid (Edema) (p 706)**

Carbohydrate Metabolism
- **Hyperglycemia (p 733)**
- **Hypoglycemia (p 733)**
- **Diabetes Mellitus (p 1246)**
- **Renal Diabetes (p 1 62)**
- **Hemochromatosis (p 1976)**
- **Hyperinsulinism (p 1242)**
- **Hypoinsulinism (p 1246)**
- **Glycosuria (p 3673)**
- **Sugar Tolerance (p 73?)**
- **Melituria (p 3676)**
- **Levulosuria (p 36,6)**
- **Pentosuria (p 3676)**
- **Lactosuria (p 36,6)**
- **Galactosuria (p 3676)**
- **Glycogen Infiltration (p 9)**
- **von Gierke s Disease (p 19,8)**

Fat Metabolism
- **Lipemia (p 738)**
- **Hypercholesterinemia (p 736)**
- **Hypocholesterinemia (p ~38)**
- **Fatty Infiltration (p 8)**
- **Cholelithiasis (p 1997)**
- **Arteriosclerosis (p 976)**
- **The Lipoidoses (p 1132)**
  - **Gaucher s Disease (p 1133)**
  - **Niemann Pick Disea e (p 1134)**
  - **Xanthomatosis (p 1135)**
  - **Hand Christian Schuller Disease (p 1137)**

Protein Metabolism
- **Albuminuria (p 2370)**
- **Proteo uria (p 3673)**
- **Azotemia (p 22~6)**
- **Hypoproteinemia (p ~06)**
- **Hyperproteinemia (p 73?)**
- **Hyperuricemia (p 37)**
- **Gout (p 2867)**
- **Albumin Globulin Ratio (p ~07)**
- **Parenchymatous Degeneration (p 7)**
- **Amyloidosis (p 7)**
- **Nephrotic Syndrome (p 2389)**
- **Uremia (p ?? 6)**

Mineral Metabolism
- **Hypercalcemia (p ,24)**
- **Hypocalcemia (p 723)**
- **Calcification (p 2,97)**
- **Decalcification (p 2806)**
- **Hyponatremia (p 729)**
- **Hypernatremia (p 730)**
- **Hyperchloridemia (p 732)**
- **Hypochoridemia (p 732)**
- **Hyperphosphatemia (p 727)**
- **Hypophosphatemia (p ,28)**
- **Hyperpotassemia (p 731)**
- **Hypopotassemia (p 731)**
- **Iodine Deficiency (p 1218)**
- **Endemic Goiter (p 1218)**
- **Iron Deficiency (p 1085)**
- **Anemia (p 1055)**
- **Acidosis (p 721)**
- **Ketonuria (p 3680)**
- **Alkalosis (p 7?2)**
- **Urolithia is (p 2311)**
- **Nephrocalcinosis (p 2314)**

Gas Metabolism
- **Carbon Dioxide Combining Power (p 720)**
- **Oxygen Saturation (p 38?7)**
- **Anoxia (p 3827)**
- **Anoxemia (p 3827)**
- **Acapnea (p 3830)**
- **Hypercapnea (p 3830)**
- **Hyperventilation (p 7??)**
- **Altitude Sickness (p 9?6)**
- **Caisson Disease (p 1501)**

Water Metabolism
- **Diabetes Insipidus (p 1180)**
- **Edema (p 706)**
- **Dehydration (p 704)**

Endocrine Metabolism
- **Hypersecretion of Acidophile Cells of Anterior Pituitary Gland (Gigantism Acromegaly) (p 1153)**
- **Hyperactivity of Basophile Cells of Anterior Pituitary Gland (Cushing s Syndrome) (p 1159)**
- **Anterior Pituitary Deficiency (Pituitary Dwarfism Frohlich s Syndrome Simmonds Disease (p 1164)**
- **Deficiency of Posterior Lobe of Pituitary Gland (Diabetes Insipidus) (p 1180)**
- **Disturbances of the Pineal Gland (p 1184)**
- **Hypothyroidism (Cretinism Myxedema) (p 1191)**
- **Hyperthyroidism (Graves Syndrome) (p 1197)**
- **Hyperparathyroidism (Osteitis Fibrosa Cystica) (p**

parts of the body structure *Metabolism* produces a steady loss of minerals in the excreta These must be replaced to maintain the constancy of the internal environment of the organism and for the proper performance of life processes

A deficiency of minerals in the diet arrests growth disturbs normal functions and gives rise to important *deficiency syndromes* (p 1218)

The *inorganic materials of dietary importance* are *sodium chloride potassium calcium phosphorus iron* and *iodine* Calcium phosphorus iron and iodine are most apt to be lacking in the diet of the average person Other elements such as *magnesium copper cobalt manganese* and *sulfur* are of comparable importance but so little is known of their physiological role that they may be disregarded for the present in practical discussions of dietotherapy

Sodium

Sodium chloride and potassium are concerned in the maintenance of normal water balance and distribution normal osmotic equilibrium normal acid base balance (physiological neutrality) and normal tissue irritability

Most of the sodium in the body is in the interstitial fluids Comparatively little is found within the cells The skeleton and cartilage have a relatively high sodium content

Sources of Dietary Sodium —The principal source of sodium in the diet is *salt* added to food for seasoning The normal diet in this country contains about 10 gm of sodium chloride a day Most natural foods are good sources of sodium Vegetables and muscle however are poor in sodium but high in potassium

Metabolism of Sodium —Sodium is absorbed from the gastro-intestinal tract and enters the extracellular fluid compartment of the body It is distributed between interstitial fluid and blood plasma Any excess is excreted in the urine The urinary excretion is regulated by the salt and water hormone of the adrenal cortex Additional amounts of sodium are lost in the sweat and in the intestinal fluids

Though sodium is pharmacologically inert it is one of the most important constituents of the human economy

Sodium and Water Metabolism —The chemical factors concerned with water movement between cells and interstitial fluid relate chiefly to *sodium potassium* and *chloride* Most of the cation of the intracellular fluid is potassium whereas sodium is the chief cation of the extracellular fluid Since potassium cannot readily traverse the semipermeable membrane it is the sodium ion which has mainly to do with osmotic pressures and hence the degree of cellular hydration

THE EFFECT OF INCREASED SODIUM ON FLUID DISTRIBUTION —The administration of *hypertonic saline solution* raises the sodium content of the extracellular fluid Isotonicity can only be restored by the passage of water from within the cell to the extracellular fluid The result is a dehydration of the individual cell This is best illustrated when shipwrecked individuals drink hypertonic sea water The result is an intensification of thirst due to cellular dehydration

THE EFFECT OF SODIUM LOSS ON FLUID REDISTRIBUTION —In the presence of excessive sodium loss there is usually a simultaneous correspond

METABOLISM IN INANITION AND STARVATION

In starvation the energy requirements are met at the expense of body tissues As one evidence of the remarkable adjustments of the human body the basal metabolic rate assumes a progressively lower level during fasting to conserve the tissues of the starving animal It is quite possible by starvation alone to lower the basal rate to —20 or —30 per cent This adjustment is utilized clinically in the treatment of the decompensated cardiac invalid by enforced undernutrition (p 912)

Oxidation of Endogenous Stores—In the absence of sufficient food the starving or undernourished animal first consumes the endogenous supply of carbohydrate chiefly in the form of muscle and liver glycogen When these are depleted the fat depots are drawn upon

The burning of fat without carbohydrate leads to the production of short chain fatty acids (beta hydroxybutyric and aceto acetic) which are intermediary normal products of the oxidation of fats These effect a reduction in the alkali reserve and an increase in the urinary excretion of ammonia

When the depot of fat is exhausted energy requirement is met at the expense of tissue protein as indicated by a rise in the urinary nitrogen excretion Each gram of urinary nitrogen represents the catabolism of 6 25 gm of protein During starvation the average daily loss of protein is 0 4 per cent of the total body protein

During starvation the tissues are drawn upon in the reverse order of their physiological importance The greatest amount of weight is lost by the fat depots (97 per cent) the spleen the liver and the muscles (31 per cent) The brain and the heart lose a relatively small proportion of their weight (3 per cent) There is a slow but steady disintegration of bone as indicated by the excretion of large amounts of calcium in the urine When starvation is protracted regressive changes occur in the endocrine glands and lead to varying degrees of endocrine hypofunction

Provided water is supplied the duration of life during starvation is amazing Professional fasters repeatedly go without food for thirty days Dogs have been fasted for 117 days and have then recovered full strength

Starvation in Relation to Dietotherapy—These general observations on starvation demonstrate the viability and the extensive compensatory mechanism present in the human economy If adequate food is not supplied by exogenous metabolism the animal will live on his own tissues Excessive limitation of protein results in the burning of endogenous protein in place of food protein An inadequate and unbalanced diet does not decrease the work of the excretory mechanism but seriously impairs the integrity of the tissues Calcium deprivation results in a conversion to a soluble form of the insoluble calcium of bone The metabolism of calcium is maintained but the structure of the bone is weakened Thus a low calcium or calcium poor diet designed to prevent the formation of calcium stones or delay calcification in an arteriosclerotic artery constitutes a well intentioned therapeutic practice but one that is inimical to the integrity of bone structure

The problem of stoking the human body is not comparable to fueling an automobile The human body can and will furnish its own fuel at the expense of body tissue It will continue to furnish it for a considerable

Therapeutic Acidosis —An excess of chloride in the extracellular fluid causes acidosis This toxicological manifestation of chloride metabolism is utilized clinically in the production of therapeutic acidosis The acidifying salts are *ammonium chloride ammonium nitrate* and *calcium chloride* The least toxic and most readily available is ammonium chloride marketed in compressed tablets of 0.5 gm dosage They may be enteric coated to prevent nausea and vomiting The administration of 3 to 4 gm daily produces a decrease in alkali reserve and favors the onset of compensated acidosis

The artificial production of acidosis has several important therapeutic applications

1 It furthers *diuresis* particularly if given with a mercurial (p 2261)
2 It lessens *premenstrual tension* and its manifestations (p 2485)
3 It tends to *offset alkalosis* (p 722)
4 It produces a highly acid urine that has *antiseptic* properties relative to certain of the bacterial invaders which survive only in an alkaline medium
5 *The excretion of the acid ion in the bronchial mucus has an expectorant effect*

℞ Liquor Ammonium Anisatus	30 0
Dropper bottle	
S g Thirty drops in ¼ glass water every 2 hours	
or	
℞ Ammonium Chloride	5 0
Syr Wild Cherry q s ad	60.0
Sig One teaspoonful every 2 hours	

POTASSIUM

In contrast to sodium which is the chief base of the extracellular fluid *potassium is the principal cation within the cells* A normal distribution of potassium ion between cells and extracellular fluid is essential for the normal functioning of the organism The amount of potassium present in the extracellular fluid (4 milliequivalents per liter) is one tenth the concentration present within the cell

Dietary Sources of Potassium —All foods contain an abundance of potassium The average intake is from 2 to 3 gm daily which is more than the body needs Muscle and vegetables are rich in potassium

In the normal individual the potassium content of the diet is of no consequence A high potassium diet may be poorly tolerated in Addison s disease uremia intestinal obstruction and fistula shock asphyxia and hemorrhage

Absorption Distribution and Excretion —Potassium is absorbed readily from the intestinal tract During periods of growth much of the dietary potassium is retained as an essential constituent of new protoplasm Any excess is excreted rapidly by the kidney which is very sensitive to the potassium content of the body fluids Excess of potassium increases neuromuscular irritability and tends to effect an increased excretion of sodium resulting in toxic manifestations

The distribution of potassium between cells and extracellular fluid is subject to several determinants The cation enters the cells during *anabolic*

tract An *average daily water loss* from each of these channels is given in the following table

Urine	1650 cc
Skin	600 cc
Lungs	450 cc
Feces	300 cc
	3000 cc

Renal elimination is delicately adjusted by the hormones and ions to maintain the volume and isotonicity of the body fluids The *insensible water loss* from the lungs and skin is intimately related to the mechanisms involved in temperature regulation It is determined indirectly according to the formula *Insensible Water Loss* = (*initial body wt* — *final body wt*) + (*weight of ingesta* — *weight of excreta*)

Distribution of Body Water —Body water is divided unequally between *intra* and *extracellular* components *Intracellular water* an integral part of the protoplasm of the cell amounts to 50 per cent of body weight It is rich in protein potassium magnesium and phosphate but poor in sodium calcium chloride and bicarbonate

Extracellular fluid constituting 20 per cent of body weight is mostly *interstitial* (75 per cent) The remaining quarter comprises the *circulating plasma* amounting to 50 cc per kilogram of body weight Compared to intracellular fluid the extracellular fluid has a relatively simple chemical structure It is rich in sodium chloride and bicarbonate poor in protein potassium and magnesium

These basic principles must be comprehended in order to realize the complexities involved in the use of water as a therapeutic agent For example if water is administered in the presence of a diminished sodium content of the interstitial fluid the cells become hyperhydrated there is no increase in the outflow of urine *water intoxication* (p 705) results On the other hand if the concentration of salt in the body fluids is excessive it is difficult to alleviate cellular dehydration by giving water The fluid is prevented from entering the cells and is promptly excreted in the urine See *Body Fluids Disturbances of* (p 702)

Interchange of Water —The interchange of water between the vascular bed and the interstices of the tissues is determined by several factors These include the work of the heart (*hydrostatic pressure*) the permeability of the vascular endothelium the osmotic pressure of the plasma proteins the lymph flow and the tension of the tissues themselves The precise manner in which each of these affects water movement is discussed in the section on edema (p 706)

Therapeutics —Water is used externally as a cleansing agent It is not absorbed appreciably through the normal skin

Diaphoretic —The tub bath increases fluid loss by favoring perspiration In advanced renal insufficiency the excretion of the accumulated catabolites may be abetted albeit feebly by the production of sweating in the hot bath or the hot pack The depletion caused by these strenuous measures far outweighs any possible benefit

Antipyretic —The evaporation of water by the skin successfully reduces

toms of an acute attack Potassium chloride is given orally in the 5 to 10 gm dose or as 50 cc of a 2 per cent solution intravenously

Potassium salts are *diuretic* The tendency for potassium to counter act retention of sodium and water has led to the use of the cation in the treatment of *Meniere s disease* (q v) Potassium salts have been also tried in the treatment of *hay fever* and other *allergic diseases* It is un likely that this is of any real value

Toxicity—An increase in potassium content of the extracellular fluids produces the picture of *acute potassium poisoning* characterized by nausea vomiting and collapse Excessively high levels lead to cardiac arrest in diastole

Hyperpotassemia is regarded by many as the factor responsible for acute vascular collapse in severe burns in intestinal obstruction and in Addison s disease Potassium salts are very toxic in patients with impaired renal function and in adrenal insufficiency

Calcium

Calcium is an important constituent of the lime salt matrix of the skeleton which contains more than 99 per cent of the entire amount of the element present in the body The small fraction not in the skeleton is of great physiological importance A constant level of calcium must be maintained in the blood to assure normal *neuromuscular function* (see *Tetany* (p 723)) The complex mechanism of *blood coagulation* requires the participation of calcium ions (See *Blood Coagulation* p 1109)

From a nutritional standpoint the chief concern of the physician with respect to calcium is to satisfy the demands for skeletal growth and repair

Neither the most satisfactory level of calcium intake nor the optimal retention of calcium in man has been ascertained

Calcium Requirement—The calcium demand is particularly large dur ing periods of active skeletal growth and during pregnancy and lactation where the maternal calcium stores must satisfy the demands of the fetus and newborn infant Up to the age of 16 the growing child requires from 1.5 to 2 gm of calcium daily In the adult skeletal growth ceases and the calcium requirement falls to about 0.5 gm daily This is the smallest amount capable of maintaining calcium balance in adult humans

During pregnancy and lactation the natural calcium requirements are about 3 gm daily This is necessary to prevent depletion of the maternal skeleton which furnishes the minerals required for the formation of the fetal bones In the absence of an adequate dietary intake of calcium the intra uterine parasite develops at the expense of the maternal skeleton which may become soft and deformed (See *Osteomalacia* p 2853)

The fetal calcium requirement is greatest during the last trimester of pregnancy During this period it is difficult to ingest sufficient calcium to remain in balance and a portion of the skeletal reserve is drawn upon

The American dietary is often deficient in calcium many individuals ingesting daily an average amount of only 0 3 to 0 4 gm This is most easily remedied by the use of foods rich in calcium such as milk and milk products particularly cheese One quart of milk yields 1 2 gm of calcium so that the normal adult is assured of his ration by the ingestion of one pint daily

of the normal diet The breakdown of 1 gm of carbohydrate (dextrose) to carbon dioxide and water produces 4 1 calories

The carbohydrates of the human diet may be subdivided into (1) those that are *unavailable* since they cannot be broken down by the digestive enzymes and (2) those that are *available* for the body in that they may be used as sources of energy and of muscle or liver glycogen

Unavailable Carbohydrates—The unavailable carbohydrates are *hemicellulose* and *cellulose* They are found chiefly in fruits and vegetables and may be grouped under the term "fiber"

The total daily intake of unavailable carbohydrate approximates 100 gm This is a very small fraction of that consumed by grazing animals

Despite their metabolic unavailability the fibers function *in the digestive tract* They provide bulk to stimulate the colon Being hygroscopic they hold water and promote easy evacuation by preventing the drying of the feces in the bowel

Though the fibers are not affected by the digestive juices they may be broken down by bacterial digestion In this process gas is formed and flatus is expelled *Flatus* is therefore a normal product of the action of bacteria on the celluloses

Available Carbohydrates—The available carbohydrates are (1) the *polysaccharides* (starch and dextrin) which are readily broken down into glucose molecules (2) the *disaccharides* (sucrose maltose and lactose) (3) the *monosaccharides* (glucose fructose and galactose)

Starch is the principal form of stored carbohydrate in plants and is found in cereals seeds and bulbs It comprises a great part of the human dietary It may be said that one half of the world lives on rice the other half on wheat

Maltose is a principal constituent of malt and germinating cereals

Lactose occurs in milk and *sucrose* in sugar cane sugar maple pineapple carrots and sugar beets Fruit and plant juices are a rich source of *glucose* *Fructose* occurs in fruit juices and in honey *Galactose* is a constituent of the *disaccharide lactose*

Sources of Carbohydrate in the American Diet—In the United States approximately 90 per cent of the carbohydrate of the diet is provided by wheat corn potatoes milk products and cane sugar

Digestion of Carbohydrate—The complex carbohydrates (poly and disaccharides) are broken down into simpler compounds by enzymes present in the digestive juices The starches are split into molecules of maltose by the action of *ptyalin* a starch splitting enzyme in the saliva This reaction is slow and takes place in a series of stages It is completed in the stomach with the aid of the hydrolytic activity of the gastric hydrochloric acid Any starch that escapes salivary digestion is rapidly converted into maltose by an *amylase* present in the pancreatic juice The maltose formed from starch is in turn split into molecules of dextrose by the action of *maltase* present in the juice of small intestine

Small intestinal juice also contains (*a*) *sucrase* which converts sucrose into dextrose and fructose (*b*) *lactase* which converts lactose into dextrose and galactose As a result of these processes all available carbohydrate is reduced to the three simple sugars (dextrose fructose galactose) which are absorbed from the small intestine

On a low calcium acid ash diet (Bauer Aub) containing 100 mg of calcium daily there is a constant loss of 60 to 100 mg daily in the urine This is increased during acidosis and in hyperparathyroidism (p 1225) In renal insufficiency the urinary excretion of calcium decreases and the intestine becomes the chief excretory path

Pharmacology—*Insoluble calcium* forms the structural basis of the bony skeleton but it is the soluble calcium ion that possesses several interesting functions

Calcium and the Clotting of Blood—Calcium is necessary for conversion of prothrombin to thrombin This step is essential for normal clotting of blood It is doubtful whether calcium deficiency is ever responsible clinically for prolonged bleeding time Hence administration of calcium salts has no significant therapeutic action in hemorrhagic diseases (p 1108)

Calcium and the Heart—Calcium has a striking effect on heart muscle under laboratory conditions An excess of this cation produces a systolic

TABLE 80—DIETARY SOURCES OF CALCIUM

AMOUNT OF DIFFERENT FOODS SUPPLYING ONE GRAM OF CALCIUM

Food	*Amount*
Milk	1 quart
Cheese	3½ ounces
Chard	1½ pounds
Cauliflower	2 pounds
Celery	3 pounds
Spinach	3 pounds
Cabbage	5 pounds
Lettuce	5 pounds
Oatmeal	3 pounds
Bread—whole wheat	4 pounds
Bread—white	8 pounds
Corn meal	12 pounds
Eggs	20 pounds
Beef	22 pounds

arrest (*calcium rigor*) The cardiac action of calcium somewhat resembles that of digitalis Hence it was suggested that calcium salts be substituted for or added to digitalis in order to augment the therapeutic effect Unfortunately this hope seems not to have been realized therapeutically The digitalis effect is best produced by digitalis alone (p 854)

Calcium and the Permeability of the Capillaries—Since calcium seems to decrease the permeability of the vessels its administration has been widely employed in exudative disturbances such as *urticaria serum rashes vasomotor rhinitis edema* and *allergic asthma* Occasionally particularly in the treatment of *angioneurotic edema* a specific therapeutic result may be obtained otherwise the administration of calcium is usually disappointing

Calcium and Tuberculosis—High calcium diets and the parenteral administration of calcium have been recommended in the treatment of tuberculosis with the hope that the increased calcium intake might lead to earlier and firmer calcification of the lesion Unfortunately no constant results have been obtained since failure of healing and calcification are

of two ways If the sensation of hunger registers and increased feedings are indulged in to an exaggerated degree an intractable type of *obesity* develops If the hunger sensation is ignored the symptoms of *hypoglycemic shock* may ensue

Oxidation of Dextrose—The burning of a molecule of dextrose in the presence of oxygen yields 6 molecules of carbon dioxide and 6 molecules of water The ratio of the oxygen consumed to the carbon dioxide produced is 1 to 1 This is expressed conventionally by the statement that the *respiratory quotient* is unity

The intermediary steps in the breakdown of glucose to carbon dioxide and water are complex and not completely known In muscle glycogen is oxidized to *lactic acid* at the completion of a series of complex transformations involving adenosine triphosphoric acid phosphocreatine and pyruvic acid Part of the lactic acid formed is oxidized to carbon dioxide and water Part is converted by muscle into *glycogen* Part diffuses into the blood from which it is removed by the liver and reconverted into glycogen

The oxidation of lactic acid to carbon dioxide and water requires the presence of a *muscle enzyme* and *coenzyme* In the absence of the *coenzyme* (thiamine) only *pyruvic acid* is formed from lactic acid thus almost completely arresting lactic acid production This step furnishes the rationale for the use of thiamine in the treatment of acidosis (p 721)

The oxidation of lactic acid provides most of the energy for muscular activity Dextrose and lactic acid are the chief sources of energy of nerve tissue The intermediary processes of carbohydrate breakdown are believed to resemble those postulated for muscle

The Relationship of Carbohydrates to Fat Metabolism—It was formerly believed that fat is not normally metabolized unless a certain amount of carbohydrate is simultaneously utilized The axiom that fats burn in the flame of carbohydrate graphically depicted this concept It was believed that the complete combustion of fat required that a gram of glucose be burned with every two or three grams of fat This ratio of fat to glucose was called the *ketogenic antiketogenic ratio*

Recent work has caused an extensive revision of the concept of ketosis The short chain fatty acids (beta hydroxybutyric and aceto acetic acid) are normal intermediate products in the combustion of fat These ketone bodies are also derived from carbohydrates and from ketogenic amino acids Ketogenesis occurs chiefly in the liver and to a minor extent in the muscles Normally the ketone bodies are completely oxidized in the peripheral tissues of both diabetic and normal animals and furnish an important source of energy This ketolytic process is not directly dependent on simultaneous carbohydrate oxidation

When carbohydrate utilization is impaired or when fat and protein metabolisms are accelerated to a great extent ketogenesis is remarkably accentuated This normal production of ketone bodies by the liver, may be greater than the ability of the peripheral tissues to oxidize them As a result, the intermediate normal products pile up in the blood stream and cause ketonemia and when the renal threshold is overstepped ketonuria results The accumulation of the ketone bodies results in a reduction of the alkali reserve with production of acidosis

High fat low carbohydrate diets are used to produce ketonic acidosis

chemical changes incident to muscular contraction Salts of inorganic phosphate comprise an important buffer system for the excretion of acid Phosphorus is a prominent constituent of the lipids (lecithin cephalin syringomyelin of the nervous system)

Phosphorus Requirement—In view of the widespread distribution of phosphorus in foods the human requirement is satisfied with ease The average daily retention in infancy is 100 mg which increases to 265 mg in adolescence The daily ingestion required amounts to about 900 mg per day Among cattle phosphorus deficiency frequently occurs and causes an intense craving for bones (*osteophagia*)

The phosphorus rich foods are cheese milk egg yolk whole wheat and meat During periods of growth and in pregnancy the phosphorus needs are increased along with those of calcium There is no definite evidence that one form of dietary phosphorus (inorganic versus organic) is superior to the other

Metabolism of Phosphorus—After absorption inorganic phosphorus is deposited in bone with calcium The ratio of calcium to inorganic phosphate in the diet is of importance in the absorption of these minerals An excess of either one augments the loss of the other The most favorable ratio of calcium to phosphorus in the diet is 2 1 The ratio varies with different stages of growth In the presence of a liberal intake of these elements the importance of the ratio becomes less

A considerable portion of inorganic phosphorus is used in the formation of phospholipids and in the intermediary metabolism of carbohydrate where phosphorylation processes are important

The parathyroid glands maintain the level of blood phosphorus and regulate the excretion of phosphorus in the urine Vitamin D affects phosphorus absorption and its deposition in bone The phosphorylation of fats to form phospholipids is controlled by the adrenal cortex The hydrolysis of phosphoric acid compounds in the body is accomplished by the enzyme phosphatase

RADIOACTIVE PHOSPHORUS

Radioactive phosphorus is produced in the cyclotron (atom smashing machine) by bombarding ordinary red phosphorus with heavy hydrogen nuclei This converts about one atom in every million to radioactive phosphorus which is called P-32 because of its atomic weight of 32 P-32 disintegrates rapidly and is excreted in the stools and urine

Pharmacology—Standard methods of x ray therapy of leukemia have the disadvantage that they are applied to local areas and thus cannot possibly eliminate all foci of the disease If generalized irradiation technics are used the dosage must necessarily be too small for the most desirable effect In an attempt to overcome these difficulties radioactive phosphorus has been used experimentally to deliver higher concentrations of radiant energy

Therapeutics—At present the use of P-32 is experimental It has a palliative effect in myelogenous leukemia (p 1101) Benefits have been noted on the spleen and nodes in lymphatic leukemia (p 1101) Acute leukemias apparently do not respond but good results have been reported in polycythemia vera (p 1093)

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hemoglobin molecule Adequate amounts of copper are supplied as contaminants of iron salts and as a food ingredient Considerable copper is stored in the body

In addition to *iron* and *copper* hemoglobin formation requires proteins of high biological value

In the presence of excessive blood loss it is practically impossible to supply sufficient iron for hemoglobin regeneration from dietary sources alone These must be supplemented by iron salts In an adult 25 mg of

TABLE 31 —APPROXIMATE IRON CONTENT OF IRON RICH FOODS

Food	*Iron Content mg %*
Vegetable	
Almonds	4
Apricots, dried	6–7
Barley entire	4–5
Beans kidney dried	7–10
lima dried	9–12
lima, fresh	2–3
Beet greens	3–4
Broccoli leaves	2–3
Chard	3–4
Dates	4–5
Figs	2–4
Oatmeal	2–3
Peaches, dried	4–5
Peas dried	6
" fresh	6
Prunes	2–5
Raisins, seeded	3–4
seedless	3–6
Spinach	3–6
Animal	
Bacon	1–2
Beef lean	3–5
Egg yolk	8
Ham	4
Lamb chops	8
Liver beef	6–8
calf	5–13
Lamb	3
Pork	20–25
Kidney	5–9
Mutton	5
Oysters	3–6

After Dauphinee.

iron are needed to increase the hemoglobin concentration of blood one per cent

Therapeutics —The therapeutics of iron is discussed in the section on the hypochromic anemias (p 1085)

IODINE

Function of Iodine —Iodine is an important constituent of the hormone of the thyroid gland which contains 50 per cent of the total iodine

calories An adequate amount of complete proteins such as those in meat eggs and milk should be guaranteed About 25 to 35 gm of protein should be derived from these sources

During periods of growth (in childhood pregnancy and lactation) the protein requirement increases to 3 gm per kilogram per day Thus the growing child requires as much total protein per day as the average adult In the aged the protein required is lowered to about 50 gm per day

The Digestion and Absorption of Protein—Protein is broken down into *acid metaprotein* and *peptones* by the action of pepsin and hydrochloric acid in the stomach In the small intestine *peptones* are further split into *polypeptides* by the pancreatic enzyme trypsin The final separation of these larger molecules into constituent *amino acids* is accomplished by erepsin of the intestinal juice

The amino acids are absorbed into the portal blood stream along with small quantities of unchanged protein peptones and polypeptides The absorption of undigested protein is most common in young children and is the basis of food idiosyncrasy in sensitive individuals (p 551)

Not all of the proteins are equally digestible The proteins of meat milk and eggs are of high digestibility The proteins of cereals are somewhat lower with the exception of wheat endosperm (cream of wheat) The protein of vegetables is least digestible

The Metabolism of Protein Products—The products of protein digestion enter the portal venous system They are transported to the liver where considerable portions are removed The rest are distributed to all of the tissues

Synthesis—The most important *process* in the metabolism of the protein products is their synthesis into *body protein hormones enzymes* and *secretions*

Deamination—The amino acids not required for synthesis are subjected to *deamination* in which the amino group is split off in the liver With deamination heat is produced This process is thought to account for the *specific dynamic action* of protein One hundred grams of meat protein increase the heat of the body by 130 calories A high protein diet such as ingested by the Eskimo maintains body warmth in cold climates It does not lead to renal damage or undue arteriosclerosis The ammonia produced by deamination is combined with the carbon dioxide to form urea which is excreted in the urine

Glucogenesis—The deaminized fatty acid radical may be oxidized or converted into glucose About 58 per cent of protein can be converted into sugar (glucogenesis) This may be stored as glycogen or fat

Deposit Protein—Not all the absorbed amino acids are incorporated into new tissues or metabolized Some are converted into reserve or deposit protein This amounts to about 2 kg and is stored in the extracellular fluid compartment

Deposit protein serves as a ready source of energy or for the replacement of essential protoplasm In fever wasting disease or starvation the amount of deposit protein decreases In myxedema deposit protein accumulates in the tissue spaces

The Sources of Protein in the American Diet—Twenty eight per cent of the protein consumed in the United States is derived from wheat and other

every obstinate clinical condition Unfortunately the efficacy of iodide in syphilis is limited to the effect on the gumma Today the gumma is a rarity in clinical practice so that the effective use of iodides has been sharply curtailed In the vast majority of instances iodide is prescribed with hope rather than any anticipation of clinical effect

Iodides and the Higher Bacteria —A specific iodide effect is observed in the treatment of infections with *actinomyces* and other mycoses (p 489)

Iodides and Tuberculosis —It is generally stated that the administration of iodide is *contraindicated in the tuberculous* It is the general belief that iodide activates the quiescent lesion Whether or not this view is correct iodide should be administered sparingly if at all in the tuberculous Should the administration of iodide be mandatory (as in the treatment of Graves disease occurring in a tuberculous patient) the proscription may be ignored since clinical experience rarely has indicated the validity of the alleged contraindication

Iodides and the Thyroid Gland —The use of iodides in the prevention and treatment of disturbances of the thyroid gland constitutes one of the most remarkable chapters in pharmacology

Iodide in the Prophylaxis and Treatment of Simple Endemic Goiter — Simple endemic goiter is a response of the thyroid gland to iodine deficiency This deficiency usually results from an abnormally low iodine level in drinking water It occurs most commonly where the water supply arises from a glacial stratum Goiter belts are therefore found in the inland mountainous and lake districts and rarely at sea level where iodine is plentiful in ocean water

As the result of the diminished iodine intake the thyroid gland undergoes a hyperplasia and an active congestion Seen in its maximum form the gland is tense and swollen the vessels engorged and the lumen of the glandular structure completely filled by hyperplastic epithelium which contains little or no colloid Clinically these changes are manifested by the appearance of the goiter (Fig 101)

The goitrous changes as observed in humans are also seen in the lower animals including particularly trout dogs and pigs The sucklings of the goitrous sow are often born dead or they die in early life of so called hairless pig malady which is analogous to human cretinism

Iodine administered in infinitesimal dosage whether taken orally rubbed in as an ointment or inhaled as fumes will prevent and relieve endemic goiter

Most important is the use of iodine in goiter prophylaxis especially amongst girls at the time of puberty and in the pregnant Under such circumstances hyperplasia of the gland may be prevented by the administration of as little as 17 mg per day or 6 6 gm in the course of a year

The mass prophylaxis of endemic goiter by the use of iodine is free from significant danger though iodide eruption occasionally will be seen in the sensitive patient

So called Iodine Basedow (Jod-Basedow) —An occasional patient receiving iodide for goiter prophylaxis or the treatment of endemic goiter develops simultaneously or concurrently an acute crisis of Graves disease (Jod or Iodine Basedow) This has been interpreted as a toxic iodide effect more apt to occur when the enlargement of the gland is due at least in

as easily digested foods for the debilitated and malnourished Since peptic and tryptic digestion are rarely inadequate these preparations possess lit tle virtue despite their great cost They may be of value in treating allergic individuals or in the care of patients with jejunostomies

Parenterally protein is most easily administered as plasma or whole blood In the treatment of hemoconcentration and hypoproteinemia (p 81) plasma is preferable

Preparations of essential amino acids (Amigen) may be given by intra venous infusion to patients unable to ingest food

Urea

Urea is an effectual *diuretic* when given in massive doses (60 to 100 gm daily) It is of especial efficacy in instances of edema without azo temia such as occur in cardiac failure nephrosis or the nephrotic stage of glomerulonephritis Because of its offensive taste urea may be given in fruit juice or with syrup of acacia The use of these massive doses may produce a moderate *azotemia* up to 100 mg of urea per 100 cc of blood Despite this there appear none of the symptoms of uremia Patients may develop a generalized *urea rash* which disappears promptly upon cessation of the drug and which may not recur on its resumption

METABOLISM OF LIPIDS

Classifications of Lipids—Fatty materials found in foods and as constitu ents of the tissues are termed *lipids* The characteristic of lipid is the fatty acid in a variety of combinations The types of combinations in which the fatty acids occur are (*a*) the neutral fats and waxes which are esters of fatty acids with glycerol and other alcohols (*b*) the *phospholipids* lec ithin and cephalin (*c*) the *cerebrosides* which contain a sugar and (*d*) *cholesterol* and the *cholesterol esters*

Composition of Fat—In the neutral fats or triglycerides the physical nature of the fat is determined by the chemical nature of the fatty acids The saturated fatty acid esters are solid while those containing unsaturated acids are liquid (oils) Most food fats contain a mixture of saturated and unsaturated fatty acids

The Metabolic Role of Lipids *Fats*—The fats are the most concentrated source of available energy yielding 9 calories per gram Certain fatty acids are essential for health and the maintenance of normal resistance to disease (*linoleic* and *linolenic* acids) Many fats used as food are rich sources of fat soluble vitamins (A D and E) Aside from its immediate nutritional value fat in the form of deposits of adipose tissue is an important in sulating mechanism against cold Vitamin K is not absorbed from the in testines unless in the presence of bile elicited by fat containing food

In the average adult about one third of the total calories are supplied from fat When energy requirement is great a larger proportion of calories is furnished from concentrated high fat foods

The absence of linoleic and linolenic acids results in a deficiency disease which is rare in humans because of the general presence of these fats

Compound Lipids—Little is known of the nutritional value of the com pound lipids (*phospholipids* and *cerebrosides*) and the *sterols* These sub stances are not essential dietary constituents and are formed as needed

Iodide and the Goiter of Pregnancy—The increased demand for iodine during pregnancy may cause the appearance of hyperplasia of the gland despite an intake of iodide that would be sufficient for ordinary needs *The goiter of pregnancy must not be accepted as a physiological accompaniment of gravidity* It should be prevented or relieved for the sake of both mother and fetus by the routine administration of iodides

Iodide in the Treatment of Endemic or Simple Goiter—The treatment of simple hyperplasia of the thyroid gland is less satisfactory than its prevention The hyperplastic gland does not revert to normal when the iodine storage has been raised to an adequate level but reverts to the colloid state The congested vessels do not completely return to normal but may remain thickened and engorged Thus when hyperplasia has existed to any great degree or for any length of time the thyroid enlargement will not disappear upon the administration of iodide The gland however will be reverted to the colloid state which is physiologically normal Secondary hyperplasia may then develop in this colloid goiter if the storage again becomes insufficient

Iodide and Thyroid Adenomas—The thyroid gland like all other glandular structures contains adenomas These adenomas function less actively than the nontumor tissue of the gland They undergo hyperplasia more readily and revert to colloid more slowly than the nontumor tissues indicating a lesser degree of activity and sensitivity

It has been suggested that the adenomas are capable of becoming toxic and producing symptomatology that their presence alters the response of the gland to iodine and that the patient with adenoma of the thyroid gland is more likely to develop toxic symptoms when iodine is administered None of these hypotheses has any justification in fact The presence of a discrete nodule or adenoma should not deter the physician from administering iodine for the purpose of converting the hyperplastic gland to the resting or colloid state

Iodide in the Treatment of Graves Disease—In true Graves disease or exophthalmic goiter the effect of the administration of iodides is usually prompt and remarkable Within the course of forty eight to ninety six hours the basal metabolic rate falls the pulse rate becomes proportionately slower the toxic symptoms abate the weight loss is stopped and the patient exhibits all of the favorable phenomena that follow subtotal thyroidectomy The mechanism of this extraordinary pharmacological reaction is far from clear The discussion of the details is more properly taken up in the section on the *Disturbances of the Thyroid Gland* (p 1186)

Unfortunately the favorable effects of iodides are not invariably observed in the patient with hyperthyroidism Some individual patients show no response whatsoever from the administration of the drug Others may experience an increase in their symptomatology during the course of iodine administration (*iodine exacerbation*) Still others after an initial favorable effect may revert to the initial symptomatology with even greater intensity (*iodine escape*)

There have been many attempts to explain the lack of success from iodine therapy in hyperthyroidism Plummer for example proposed the hypothesis that the favorable effects were limited to patients with diffuse hyperplasia while the unfavorable results were observed in patients with

Choline seems to stimulate the formation and liberation of phospholipids in the liver It causes a rapid subsidence in the degree of fatty infiltration of the liver when given orally to depancreatized dogs Both choline and its derivative betaine are effective in reducing the size of the fatty livers in severe diabetics

Storage of Fat—Most of the diet fat is deposited in storage depots before it is utilized The chief depots are the *subcutaneous tissues* the *omentum* and the *mesenteries* Much fat is stored in the liver but this is entirely for immediate metabolic use

Depot fat is usually characteristic in composition for each species and depends on the dietary habits When diets containing unusual types of fatty acids are fed to experimental animals the composition of the depot fat will resemble the diet fat There is a steady turnover of fat in the depots and deposited fat is utilized within two to three weeks

Oxidation of Fatty Acids—Fatty acids are completely oxidized to carbon dioxide and water The process requires more oxygen than in the case of carbohydrates and the respiratory quotient accordingly is low (0 7) When a large portion of the energy requirement is being furnished by fat as in diabetic ketoses starvation or a high fat (ketogenic) diet the fatty acids are not completely oxidized and large amounts of ketone bodies (short chain fatty acids) appear in the blood

The Sources of Food Fat in the American Dietary—The sources of food fat in the United States are pork (40 per cent) dairy products including butter and cream (27 per cent) oils (10 per cent) beef (10 per cent) poultry and eggs (3 per cent)

When the melting point of the fat is high digestion is slower and there is the tendency for the excess fat to appear in the feces

Therapeutics—*Low fat diets* are employed to reduce the caloric intake since weight for weight the fats provide twice as many calories as protein and carbohydrates Fat poor diets are also used where there is a tendency to form gallstones Paradoxically while the lipids favor the deposition of cholesterol crystals which form the nucleus of the gallstone the ingestion of fat promotes emptying of the gallbladder as is well illustrated in the diagnostic dye test of gallbladder function (p 1988)

The *high fat diet* is employed to increase the caloric intake (p 699) To prevent acidosis the ratio of fat to carbohydrate intake must not exceed 3 1

In the *ketogenic diet* a higher fat ratio is deliberately employed in order to produce a therapeuitc acidosis (p 599) through inadequate combustion of the fat

While the metabolism of *cholesterol* and *lecithin* have many interesting academic connotations they possess no particular therapeutic efficacy to the extent of our present knowledge Cholesterol for example is closely related chemically to vitamin D and the steroids of endocrine importance Lecithin similarly has many interesting chemical affinities none of which is as yet therapeutically fruitful

There is as yet no method of administering fat parenterally

METABOLISM OF MINERALS

Inorganic elements constitute important dietary essentials *Growth* is associated with an increased demand for these substances which are integral

The treatment of iodism is the cessation of the drug and the liberal administration of fluids and sodium chloride

MAGNESIUM

Magnesium is present in small concentration in the blood (4 mg per 100 cc) It is of considerable physiological and pharmacological importance It plays an important part in muscle metabolism and in the activation of animal phosphates

Pharmacology.—The magnesium salts may be employed locally on the skin and *mucous membranes as local anesthetics* and *anti inflammatory agents* Given enterally they are antacid laxative and somewhat anti spasmodic Systemically magnesium depresses smooth muscle and nervous tissue so that it may be employed as an *anti-convulsant* and an *analgesic* Studies of bound and unbound blood magnesium have indicated the importance of this cation in the pathological *physiology of hyperthyroidism* As yet however this information has no therapeutic implications

Preparations —*Magnesium sulfate* is employed locally in 25 per cent solution enterally as *Epsom salts* for laxative purposes and systemically in 25 to 50 per cent solution for intramuscular injection as an antispasmodic and analgesic As a saline laxative magnesium sulfate is used in dosages of 15 gm (4 drams) For parenteral use the maximum dose should be 0.5 to 1 0 gm (2 to 4 cc of a 25 per cent solution or 1 to 2 cc of 50 per cent solution) Since the toxic effect of the magnesium ion is sudden paralysis of the respiratory center the systemic use should not be hazarded unless there is available for ready injection a preparation of the soluble calcium salts which act as a pharmacological antidote (p 2387)

*Magnesium citrate is used exclusively as a laxative The citrate is com*monly prescribed as a solution containing free citric acid saturated with carbon dioxide and marketed in firmly stoppered bottles containing 350 cc The dosage varies from 200 to 350 cc (7 to 12 fluidounces)

Magnesium oxide magnesium carbonate and *magnesium trisilicate* are antacids and absorbents *The oxide is* prescribed in dosages of 0 25 gm (4 grains) the carbonate in 0 6 gm (10 grains) the trisilicate in 1 to 4 gm (15 to 60 grains) quantities

Therapeutics —For *local action on the skin* saturated magnesium sulfate is employed as an *anesthetic* and *anti inflammatory agent* Its efficacy is of questionable value beyond that of any wet dressing

Enterally magnesium salts have a variety of indications As *antacids* and *absorbents* magnesium oxide magnesium carbonate and magnesium trisilicate are of considerable value In addition to the local effect on the stomach they also function as saline laxatives in contradistinction to the calcium salts which effect or favor constipation (p 1830)

Instillations of 25 per cent magnesium sulfate through the duodenal tube are employed in the management of obstructive jaundice *Presum*ably the drug relaxes the *sphincter of Oddi* producing a nonsurgi drainage of the bile duct The magnesium salts particularly the sulfate the oxide (*milk of magnesia*) are popularly favored as *saline* Most of the laxative waters of the various spas depend for their upon their content of magnesium sulfate

The *parenteral use* of 25 or 50 per cent magnesium sulfate has

ing loss of water and a diminution in extracellular fluid volume (including plasma volume) accompanied by a progressive hemoconcentration and eventual peripheral circulatory failure This type of disturbance may be encountered as a result of vomiting diarrhea a biliary or intestinal fistula and in adrenal insufficiency In the latter however in addition to the excessive loss of sodium and water in the urine there is a passage of sodium and water into the cells which further increases the shrinkage in extracellular fluid volume (p 702) If water is given in the above circumstances without sodium it passes quickly into the intracellular compartment and produces intoxication within the cell in the presence of extracellular dehydration This is well illustrated by miners cramps which commonly follow the ingestion of water without salt after a period of violent exercise and profuse sweating

Therapeutics —Sodium replacement is required with loss of body fluids and in adrenal cortical deficiency

Loss of Body Fluids —Those who suffer from excessive water loss (sweating diarrhea vomiting and the glycosuria and acidosis of diabetes mellitus) should be given saline solution rather than water alone to avoid osmotic disturbances Empirically many athletes and trainers miners and steel workers who sweat considerably during their labors have learned to lick salt

Addison s Disease —In the acute crises of adrenal cortical insufficiency sodium chloride is given in daily doses of 10 to 20 gm This simple therapeutic measure helps prevent and relieve the urgent symptoms of the *acute crises* (p 1275) by restoring the salt content of the *extracellular* fluid

Administration —Sodium is supplied as the chloride administered orally as table salt or in capsules Parenteral sodium may be administered as physiological saline (0 9 per cent), or Ringer s or Hartmann s solutions (sodium r lactate) The last is preferable in cases of acidosis The lactate is oxidized to carbon dioxide and water leaving the basic sodium ion

Chloride

Function of Chloride —Chloride is the chief *acid radical* (*anion*) of the body fluids It is intimately bound to sodium It is especially abundant in the extracellular fluid and is found where the interstitial water is greatest (skin blood muscle bone connective tissue)

The functions of chloride are similar to those of sodium namely the maintenance of acid base balance osmotic equilibrium and normal fluid passage between the cells and the extracellular fluid In addition chloride is a precursor of the hydrochloric acid of the gastric juice

Dietary Chloride —All foods are rich in chloride ion It occurs in combination with sodium or potassium

Metabolism of Chloride —Upon ingestion chloride enters the blood and quickly passes to the interstitial fluid compartment It is then slowly excreted during the next six to twenty four hours When an excess is ingested it is excreted in the urine In the presence of a deficiency chloride disappears from the urine

Therapeutics —Chloride has little pharmacological action It is amply and adequately supplied in the dietary and it is satisfactorily absorbed stored excreted and assimilated Its major functions refer to the *alterations* produced in osmotic pressure

VITAMIN A

Vitamin A has been isolated from natural sources and has also been prepared synthetically The carotenes and a carotenoid precursors of vitamin A are widely distributed amongst foodstuffs most particularly those that possess rich pigmentation Beta carotene is commercially available in oily solution dispensed in soft gelatin capsules It is readily transformed into utilizable vitamin A in the body

Daily Requirement—The daily requirement for the normal individual varies with age occupation basal metabolic rate lactation and pregnancy

Unitage—The U S P unit of vitamin A equivalent to the international unit is the amount in milligrams that produces the growth promoting and anti-ophthalmic activities equal to that of 0 6 micrograms of the international standard beta carotene or the equivalent amount of U S P Standard Reference Cod Liver Oil

Food Sources.—The important food sources of vitamin A include many articles of food utilized in the normal diet The most important are whole milk and milk products eggs peas green beans green peppers parsley stocks asparagus carrots sweet potatoes apricots peaches bananas tomatoes and yellow corn

Functions of Vitamin A—Vitamin A is essential in the transformations of visual yellow to visual purple under the influence of dark The visual

TABLE 83—AVERAGE DAILY REQUIREMENTS OF VITAMIN A FOR THE NORMAL INDIVIDUAL

Infant and child	1500–4500 units
Adolescent and adult	4000 units minimum
Adult	5000 units
Pregnancy and lactation	6000–8000 units

U.S.P units

yellow depends on the synthesis of vitamin A and a protein Besides its relation to night vision vitamin A is necessary for the normal metabolism of epithelium its deficiency causing keratinization

The Absorption Utilization and Excretion of Vitamin A—Vitamin A is readily *absorbed* from the normal gastro intestinal tract Excesses are excreted in the feces

Because of its fat solubility the absorption of vitamin A is dependent somewhat upon the presence of bile in the intestines Despite an adequate dietary intake vitamin A deficiency may result during *obstructive jaundice*

After absorption vitamin A is *deposited* and stored in the liver The provitamin carotene is *converted* to active vitamin A in this organ In diseases of the liver and diabetes this conversion may not occur and deficiency symptomatology may result despite adequate intake Vitamin A may be stored in the liver for several months in contrast to the transient storage of water soluble vitamins

Vitamin A is partially *destroyed* in the body Under special conditions it may be lost through the excreta Thus the ingestion of liquid petrolatum in which the vitamin is soluble increases the output in the stool Steatorrhea also causes washing out of the ingested vitamin The absence

processes (growth rest) and leaves them during periods of tissue break down (*catabolism*) i e increased metabolism exercise starvation The excessive loss of sodium from the body (as seen in severe burns intestinal obstruction, adrenal insufficiency and acute hemorrhage), causes potassium to pass out of the cells and accumulate in the plasma

The adrenal cortex regulates the renal excretion and the distribution of potassium and sodium in the body Potassium accumulates in the extra cellular fluid in *adrenal insufficiency* The administration of excessive amounts of desoxycorticosterone an adrenal cortical hormone causes an increased renal excretion of potassium and the replacement of muscle potassium by sodium Clinically this chemical change and a *decrease* of serum potassium concentration produces a form of periodic paralysis (p 1416)

Pharmacology —Potassium bears an intimate relation to the normal functioning of the nervous system skeletal and cardiac muscle and the kidney

Relation to Nerve Impulse Transmission —An increase in potassium ion concentration reduces the excitability of peripheral nerves and may even block conduction This effect enhances the action of local anesthetics and the anesthesia produced by cold Potassium salts are known to potentiate the action of local anesthetics The potassium ion evidently is involved in the neurohumoral transmission of autonomic nerve impulses The cation is concerned in some way with the activity of both acetylcholine and epinephrine

Cardiac Action —The normal rhythmicity of mammalian cardiac muscle requires an optimal concentration of potassium ions In the absence of potassium the isolated heart stops in systole An increased concentration of potassium has a direct depressant action on cardiac muscle and stops the heart in diastole

Skeletal Muscle —The contractibility of skeletal muscle is altered in some obscure fashion by changes in potassium ion concentration Some of these effects are due to changes in the nerve impulse transmission and the liberation of chemical mediators Potassium salts prevent attacks of *periodic paralysis* tend to relieve some of the symptoms of *myasthenia gravis* and overcome the action of curare The muscle weakness of desoxy corticosterone overdosage is relieved by potassium salts

Diuretic Action —Potassium salts frequently are effective diuretics in cases of generalized edema They appear rapidly in the urine and are completely rejected by the tubules An increase in the potassium concentration of the body fluids tends to cause a potassium diuresis A potassium diuresis is also caused by large doses of desoxycorticosterone This is attended by a form of hyposthenuria in which the renal action of pituitary antidiuretic factor is impaired

Preparations —Potassium is given therapeutically as the *chloride* or the *nitrate* Both salts are freely soluble in water and have a saline taste Many potassium salts are used for the action of the anion rather than the potassium they contain i e potassium permanganate and potassium iodide

Therapeutic Uses —Despite its important physiological implications potassium serves little therapeutic purpose Potassium salts are employed to prevent the attacks of *familial periodic paralysis* and to relieve the symp

of bile in the intestines as mentioned above results similarly Vitamin A is eliminated in the milk hence the nursing mother must be given more than the usual adult dosage

Deficiency of Vitamin A—The *severer manifestations* of vitamin A deficiency are rarely seen clinically They may be produced experimentally in the laboratory animal Occasionally they are found in individuals who suffer great deprivation or who have a dietary deficiency as the result of a profound or severe intestinal disease impairing absorption

Milder degrees of A deficiency are encountered clinically in increasing numbers dependent upon the care with which the changes are sought and the accuracy with which they are interpreted Patients who complain of *photophobia* and *poor adaptation to dark* are suspects They may be more accurately tested by the biophotometer or vitamin A blood level Individuals with the characteristic skin changes should be subjected to the therapeutic test

A marked reduction in the availability of vitamin A produces symptomatology referable to the *epithelial structures* and to the *visual apparatus* The commonest and most dramatic symptom of avitaminosis A is *nyctalopia* or *night blindness* Clinically this becomes apparent most readily in individuals who while motoring are blinded by exposure to glaring headlights or who cannot see the film for a period of as long as fifteen minutes after they have entered a darkened motion picture house Presumably vitamin A functions in the resynthesis of visual purple Its lack interferes with this reaction and results in nyctalopia (p 1532)

Continuance of vitamin A deficiency leads to *xerophthalmia* characterized by keratinization of the cornea and eventually to *ulceration* Similar epithelial changes may occur in other cutaneous and mucous surfaces Thus the skin becomes dry and develops *hyperkeratosis* particularly noted around the openings of the sweat and sebaceous glands The *bronchial epithelium becomes cornified* resulting in a high incidence of respiratory infection The changes in the epithelium of the urinary tract lead to development of *calculi* The dental enamel may become imperfect and lead to frequent *dental caries*

In a more general way vitamin A deficiency retards growth and development

In addition to the therapeutic indications for the administration of vitamin A in the treatment of the specific deficiency states attempts have been made to broaden the usages by administering the substance as a preventative of infection (anti infective vitamin) in the treatment of all types of *hyperkeratosis* to supplement the management of patients suffering from *urinary calculi* in the treatment and prevention of *dental caries* in the treatment of chronic *metabolic arthropathies* (p 2855)

It is extremely doubtful whether the administration of vitamin A has any particular utility in conditions other than specific avitaminosis Excessive intake of carotene may result in a pigmentation of the skin resembling jaundice (p 1951)

The prophylactic use of vitamin A is justified Increased amounts should be fed to infants and growing children to lactating mothers and to patients who suffer from any hepatic disease particularly one associated with jaundice

Absorption of Calcium—Calcium is readily absorbed in the small intestine The amount absorbed depends on a variety of factors of considerable practical importance

In general the availability of ingested calcium is decreased by substances which tend to precipitate it and is favored by those which keep it in solution An excess of fat an extremely high or low intake of phosphorus and a lack of vitamins C and D interfere with the absorption of calcium

Calcium absorption is favored by an acid medium and hindered when the reaction is alkaline Large amounts of unabsorbed fatty acid in the intestinal tract interfere with absorption since insoluble soaps are formed Absorption is also impaired in diarrheal conditions so that in spite of an adequate intake hypocalcemia occurs

Even when conditions are favorable only a small fraction of the total dietary calcium is absorbed the remainder being excreted in the stool as insoluble calcium compounds In view of this an adequate dietary intake requires an overabundance of calcium containing foods Individuals vary tremendously in their ability to utilize the calcium from their foods They may utilize as little as one fifth of the calcium in milk and generally absorption does not exceed 50 per cent of the intake Certain vegetables namely carrots lettuce and stringbeans tend to depress calcium utilization The utilization of the calcium from oatmeal and spinach is particularly poor

The Metabolism of Calcium—The calcium content of normal human serum approximates 10 milligrams per 100 cc The blood corpuscles contain only an insignificant amount of calcium The remainder is present in the serum Half to two thirds of the serum calcium is diffusible the rest being nondiffusible

The Stores of Calcium in the Body—The largest store of calcium is present in the *skeleton* Bone contains 60 per cent of calcium in combination with phosphate and carbonate The remainder of the body calcium is largely in the extracellular fluid

The calcium of the *serum* is present (1) *in true solution* in combination with serum protein and (2) as a *supersaturated solution* of calcium phosphate or calcium carbonate Only the true soluble calcium is *ionized*

Calcium absorbed from the gut is quickly deposited in bone as part of a complex salt of calcium phosphate and carbonate This serves two purposes It acts as a rigid framework to protect the soft tissues and affords fixed points for the attachment of muscles and ligaments It also is a storehouse for readily available calcium which is liberated from the bony trabeculae in response to metabolic demands

The metabolism of calcium is dependent upon factors other than dietary intake and excretory output Normal calcium economy is regulated by parathyroid hormone vitamin D the metabolism of phosphate and bicarbonate and the reaction of the blood and tissues The deposition of calcium and phosphorus in bone requires the participation of *vitamin D* In its absence calcification cannot occur and the bone is soft and rachitic (p 2850)

The dissolution of bone into calcium and phosphate ions *is controlled* by the parathyroid hormone which maintains a physiological level of calcium and phosphorus in the blood (See *Parathyroids* p 1223) Decalcification also occurs during acidosis

ing the blood phosphate and permitting mobilization of calcium from the bone Thus the blood calcium level is secondarily increased Calcium and phosphorus function reciprocally

The use of excessive amounts of vitamin D may produce calcification *in the renal tubules the blood vessels and the heart*

Deficiency of Vitamin D—Deficiency of vitamin D produces the familiar picture of *rickets* (p 2850) in infants and growing children and of *osteomalacia* (p 2853) in the adult (Fig 105)

In rickets large amounts of unabsorbed calcium and phosphorus are excreted in the stool The blood phosphate is reduced though the blood calcium level is maintained due to a compensatory hyperfunction of the parathyroid gland The high calcium or normal calcium level and the high fecal calcium result in a withdrawal of calcium from bone and the production of the familiar clinical symptomatology of infantile rickets

Therapeutics—Vitamin D is employed primarily in the prophylaxis and treatment of rickets The *prophylactic* administration of vitamin D should be initiated in the third week of life The dosage is approximately 200 units daily By the end of the first month the child should be receiving 800 units daily In the *treatment* of rickets the curative dose approximates 1200 units daily but considerably more may be administered with safety Infantile tetany associated with rickets will also respond to vitamin D although the urgent symptoms should be treated with calcium The continued use of vitamin D should then prevent recurrence

Official Preparations and Dosage—The official preparations of vitamin D are *irradiated ergosterol* containing vitamin D alone the *fish liver oils* containing both vitamins A and D and the *fish liver oils with added irradiated ergosterol* in which the content of vitamin D proportionates the content of vitamin A

The international unit of vitamin D possesses the activity of 1 mg of an international standard solution of *irradiated ergosterol* equal in potency to 0 025 mg of *calciferol* (crystalline vitamin D) The *U.S.P unit* is the equivalent of one international unit

The activity is tested on standard rats who have been given experimental rickets

Activated ergosterol in oil U.S.P contains 10 000 units of vitamin D per gram *Viosterol in oil N.N.R* is prepared similarly Neither of these preparations contains vitamin A

Cod liver oil U.S.P contains a minimum of 85 units of vitamin D per gram *Halibut liver oil N.N.R* is richer in vitamin D and assays at 540 units per gram The *percomorph liver oil is the richest source and yields 8000 units of vitamin D per gram thus being a fine source of both A and D* It is the preparation of choice

The N.N.R preparations include cod liver oil and halibut liver oil with added viosterol The former must contain 360 units per gram the latter 9000 units per gram

One of the many irradiation products of ergosterol is *dihydrotachysterol* (*A T 10*) A T 10 is so closely similar physiologically to the parathyroid hormone that it may be used in the treatment of parathyroid deficiency with an equally efficacious therapeutic effect It promotes the renal excretion of phosphorus thus lowering the phosphate content of the blood

rarely if ever, dependent upon a deficient calcium intake The same condition is observed in trichinosis

Preparations —Soluble and insoluble salts of calcium are employed in therapeutics

Soluble Salts—The soluble salts calcium chloride U.S.P calcium gluconate, U S P and calcium lactate U S P are used for their specific ion effect

Calcium chloride contains 27 per cent of calcium It is freely soluble in water and highly irritating It may be injected intravenously in 5 to 10 per cent concentration The injection rate must not exceed 1 cc per minute and the total dose should not exceed 1 gm

Calcium gluconate contains 9 per cent of calcium It is a white powder that is much less irritating to the tissues than calcium chloride It may be given orally in doses of 5 gm A 20 per cent aqueous solution may be injected intramuscularly or intravenously The total dosage must not exceed 1 gm (5 cc of the 20 per cent solution)

Calcium lactate contains 13 per cent of calcium It resembles the gluconate and may be used interchangeably with that salt

Insoluble Salts—The insoluble salts of calcium include precipitated calcium carbonate U.S P tribasic calcium phosphate U S P and calcium phosphate B P

The *precipitated calcium carbonate* or chalk forms the basis of most *tooth powders* The antacid salts of calcium are nonsystemic antacids Unlike the magnesium salts they tend to produce constipation rather than a laxative effect

Therapeutics —The *insoluble calcium salts* are used for their *detergent* and *antacid* effects The *soluble calcium salts* are employed in the treatment of *low calcium tetany* as antispasmodics in the treatment of *colic* and in the control of the *exudative disorders* such as urticaria (p 3345)

In *parathyroid deficiency* the use of calcium is futile without the administration of parathyroid hormone With vitamin D deprivation therapy is aimed at correcting the deficiency rather than increasing the calcium intake Calcium is employed by the pediatrist to obtain a finer clot in the milk used for *infant feeding* The addition of lime water to the milk insures a uniform soft curd Intravenous injection of calcium salts is occasionally effective as an antipruritic

PHOSPHORUS

Phosphorus is an essential constituent of protoplasm It is present in all the body cells and fluids and in all natural foods Phosphorus occurs in the body as *inorganic phosphate* as part of complex organic compounds i e *phosphoproteins nucleoproteins phospholipids* and in combination with *creatine* and *carbohydrates* Seventy per cent of the retained phosphorus combines with calcium while the remainder combines with nitrogen

The functions of phosphorus in the body are many It is used in the construction of nervous muscular and skeletal tissue Along with calcium and carbonate inorganic phosphate is a constituent of bone which contains 80 per cent of the body phosphorus Phosphoric acid is intimately involved in the *metabolism* of *protein fat* and *carbohydrate* It enters into the

severe nutritional disturbances such as profound diabetes pregnancy toxemia and chronic alcoholism Most often the patient has initial neurologic manifestations such as pain weakness and cramps in the legs later numbness and paresthesias are observed With advance in the neuromuscular difficulties there may be foot drop and awkwardness in gait and eventually the arms become involved with wrist drop The mental symptoms of thiamine deficiency are most complicated and may resemble such syndromes as delirium tremens and the Korsakoff psychosis the patient is confused deteriorated and may hallucinate (p 3851)

The cardiovascular symptoms of thiamine deficiency may dominate the clinical picture There may be a generalized dilatation of the heart arteriolar dilatation manifested by redness and warmth of the skin backward failure and the development of edema (wet beriberi) Usually in association with these there are abnormalities of the digestive tract such as anorexia nausea soreness of the mouth dysphagia vomiting and constipation Carbohydrate metabolism shows a change toward the diabetic side and a sugar tolerance test is characterized by a marked and sustained hyperglycemia (Fig 105)

Therapeutics—The principal use for thiamine chloride is in the correction of definitive deficiency where startling results are obtained with great rapidity Less clear are the symptomatic benefits that follow intravenous thiamine therapy using large doses (100–200 mg) in conditions such as the crises of tabes dorsalis and vague neuritic psychiatric digestive and cardiovascular disturbances These favorable experiences cannot wholly be dismissed as psychogenic They are sufficiently impressive to warrant a therapeutic trial under any circumstance

Preparations—*Thiamine Chloride U.S.P* is available for oral use in the form of tablets containing 1 mg or more of the substance It is also dispensed in elixirs of various strengths

For parenteral use sterile ampoules or rubber stoppered vials provide solutions varying in strength from 10 to 100 mg per cc The more concentrated solutions are slightly irritating by subcutaneous injection If the intravenous route is not employed the solution is best given intramuscularly

Riboflavin—Riboflavin the second member of the B complex has also been termed vitamin B_2 or G It is chemically related to the sugar *d* ribose It is available in crystalline synthetic form for therapeutic purposes

Dietary Sources and Requirements—Riboflavin occurs abundantly in milk cream cheese eggs liver kidney animal entrails and vegetables such as the legumes broccoli soy bean and turnip greens It is also found in yeast bran crabs oysters sardines and strawberries The daily requirement has been estimated at between 2 and 3 mg

Physiology—Because it is a constituent of the yellow respiratory enzyme riboflavin fulfils an important function in cellular metabolism It probably occurs in all cells The vitamin is slowly destroyed in the body some being excreted in the urine and (during lactation) in the milk Little is stored in the organism

Riboflavin Deficiency—Isolated riboflavin deficiency is rare It is usually associated with disturbances of other members of the B complex The manifestations that may be attributed to *ariboflavinosis* include burning

rarely if ever, dependent upon a deficient calcium intake The same condition is observed in trichinosis

Preparations—Soluble and insoluble salts of calcium are employed in therapeutics

Soluble Salts—The soluble salts calcium chloride USP, calcium gluconate, USP and calcium lactate, USP are used for their specific ion effect

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and itching of the eyes photophobia lacrimation rapid visual fatigue blurring of vision impairment of distant vision and inability to see in the dim light Examination reveals congestion or inflammation of the con junctiva evidences of interstitial keratitis and vascularization of the cornea the corners of the eyes may become fissured and cracked

Associated with the eye changes there is superficial fissuring and ulcera tion at the corners of the mouth in the nasolabial folds in the nostrils or behind the ears the tongue is characteristically purple and has a peb bled or granular appearance there may be fissuring of the tongue caus ing *burning sensations and dysphagia the skin over the bridge of the* nose has a shark skin appearance there may also be scaling of the hands and perineum (Figs 106 107)

Preparations—Riboflavin N.N R is available in crystalline form and in ampoules which contain 1 mg per 2 cc of 10 per cent urea solution

Niacin or Nicotinic Acid—Nicotinic acid is a portion of the vitamin B complex (*pellagra preventive factor*) Its chemical name is pyridine 3 car boxylic acid It is related chemically but not physiologically to nicotine possessing none of the toxicity of the latter Nicotinic acid may be pre scribed as the amide or the sodium salt

Dietary Sources and Requirements—In nature nicotinic acid is found in wheat germ yeast and the animal entrails such as liver kidney heart or the animal muscle meat as well as salmon It is also found in canned peas turnip greens and peanut meal

The daily requirement of nicotinic acid approximates 25 mg

Physiology—Nicotinic acid functions as a constituent of certain co enzymes in the promotion of *cellular oxidation* It is readily absorbed via the enteral and parenteral routes and is excreted in the urine

Excessive doses of nicotinic acid particularly by the intravenous route give rise to a *vasodilatation that may last for a few hours* Simultaneously the patient may complain of itching and burning The cutaneous tempera ture rises These symptoms do not occur when the amide form is given Doses far above the therapeutic level produce convulsions and death in dogs

Niacin Deficiency—The subclinical symptoms of niacin deficiency are similar to those of deprivation of thiamine Personality changes however appear to occur earlier and include indifference forgetfulness insomnia headache vertigo apprehension and palpitation Some of the patients have predominantly digestive symptoms such as anorexia nausea flatu lence and diarrhea With more advanced or prolonged deficiency the patient approaches or develops the syndrome of *pellagra* The gastro intes tinal manifestations are predominantly those of a glossitis there is swell ing and redness of the tip and lateral margins of the tongue later there may be ulceration with the formation of a greyish membrane that pre disposes to a complicating *fusospirochetosis* (p 355) Other mucous mem branes notably in the esophagus stomach small bowel and anus de velop similar changes so that the patient may also complain of dysphagia gastric distress diarrhea rectal tenesmus and bleeding

The skin changes are dependent in their extent upon the factor of exposure to sunlight The in door pellagrin reveals little abnormal those who are exposed to sunlight show pigmentation of the exposed areas

Iron

Iron as an important component of hemoglobin is necessary for the transport of oxygen to the tissues by the red blood cells In addition it is an essential constituent of the cellular enzyme (*cytochrome*) which takes part in the intracellular oxidation reduction reactions It also occurs in muscle hemoglobin the function of which is not known and which cannot be drawn upon by the organism in anemia

Iron Requirement—The normal *adult* requires about 15 mg of iron daily The requirement is greater in *childhood* and during *pregnancy* The *normal infant* at birth possesses sufficient stored iron to supply the amount needed during the first six months of life At the end of this period additional amounts must be obtained in the food

Full term infants born of anemic mothers and *premature infants* have little reserve iron and require large amounts of dietary iron early in life

With the onset of *menstruation* the iron requirement of the female is almost doubled

Dietary Sources of Iron—The iron content of food is highest in green leafy vegetables beans and peas in meat muscle and glandular tissues and in eggs Among meats liver is richest in iron Whole wheat bread contains twice as much iron as white bread This is because most of the iron in grain is contained in the outer covering which is removed during milling

Milk a perfect food in most other respects contains very little iron—about 0 02 to 0 05 mg per 100 cc Infants kept exclusively on a milk diet are prone to develop nutritional anemia (*milk anemia*) when their endogenous iron stores are depleted

Absorption of Iron—Iron is absorbed in the duodenum The simple salts are absorbed in the form of *ferrous* iron Ferric iron is probably reduced in the intestinal tract to the ferrous form Absorption is assisted by hydrochloric acid which renders dietary iron soluble

Adults with gastric anacidity have difficulty in absorbing iron and unless large doses of iron salts supplement the diet often develop iron deficiency (nutritional) anemia The presence of large amounts of phosphate in the intestinal fluids and of alkalinity interferes with the absorption of iron

Only a portion of the iron present in food is available The greater part chiefly organic iron containing compounds is poorly utilized and excreted in the stool Ingested hematin iron is not available for utilization by the animal organism

Metabolism of Iron—Iron absorbed as ferrous salts is transported as ferric iron in the plasma The liver acts as the principal depot for iron which is liberated to satisfy the requirements of the bone marrow for hemoglobin formation Iron obtained in the break down of red blood cells is retained in the body while the iron free pigments biliverdin and bilirubin are excreted in the bile The hemoglobin breaks down into globin and hematin and the latter into hemosiderin and the iron free pigments

Relatively little iron is excreted That which appears in the stool is unabsorbed ingested iron The small amount which is excreted appears principally in the bile

Small amounts of *copper* are necessary for hemoglobin formation The copper acts as a catalyst for the introduction of inorganic iron into the

Pyridoxine—Pyridoxine is a component of the vitamin B complex A deficiency of this substance produces edema and ulceration about the ears pores and snout of rats and changes in the hair matrix The chick requires pyridoxine for normal growth Intrathecal injections of 30 to 50 mg are reported beneficial in the scleroses tabo paresis chorea and poliomyelitis

Choline—Choline is another factor in the water soluble vitamin B complex Its pharmacology has been elsewhere described (p 3873) These consist briefly in a stimulation of the para sympathetic nerve endings (cholinergic) as well as a preliminary stimulation followed by paralysis of the ganglia of the involuntary nervous system From the metabolic standpoint choline prevents excessive deposit of fat in the liver It alleviates fatty infiltrations of the liver and hence has been termed a lipotropic substance Experimentally choline is important in the methylation of homocystine to form methionine This function forms the basis for the use of choline in hepatic diseases such as the cirrhoses (p 1969)

Inositol—Inositol is a factor that prevents baldness in the mouse This anti alopecia substance differs from pantothenic acid Inositol also possesses lipotropic properties and prevents the development of acutely fatty livers and the accumulation of cholesterol in the liver in experimental rats

Para Aminobenzoic Acid—Para aminobenzoic acid appears to prevent the graying of hair in experimental animals (cats) This principal has been termed achromotrichial factor It will be recalled that para aminobenzoic acid inhibits the bacteriostatic property of the sulfonamides Hence the use of the preparation is to be avoided in patients treated with these drugs

VITAMIN C

Vitamin C known also as the *antiscorbutic vitamin cevitamic or ascorbic acid* has been isolated in pure form It is a water soluble substance

Sources—The foods containing appreciable quantities of vitamin C are lemons *oranges grapefruit tangerines tomato juice raw cabbage* water cress fresh strawberries and red peppers Since oxidation occurs readily foods may easily lose their ascorbic acid potency Thus for example orange juice should be freshly prepared before consumption and not allowed to stand over night Orange juice may contain as much as 0 5 mg ascorbic acid per cc

Physiology and Deficiency—Ascorbic acid is a strong reducing agent Hence it probably has some function in cellular metabolism though this has not as yet been conclusively demonstrated Of more immediate clinical importance is its function in preserving the integrity of certain cells derived from mesenchyme and their intercellular substance It is the defect of intercellular cement substance in the capillaries which produces the hemorrhagic manifestations of scurvy These include bleeding into joint spaces beneath the periosteum from the gums nose and subcutaneous tissues as well as changes in the teeth and defects in growing bone

The administration of this vitamin is specific in prevention and cure of the syndrome whether it occurs in infants or adults Vitamin C has also been given for a variety of other conditions with indifferent and variable results Its prime indication is still the scurvy syndrome Vitamin

content of the body (10 mg) It is essential for the calorigenic activity of thyroxin

When the iodine content of the gland is reduced the normal gland becomes hyperplastic the vascularity of the gland is increased and an enlargement or goiter develops (p 1204)

Iodine Requirements—Normal iodine requirements are small, varying from 0 05 to 0 10 mg daily An increased demand for iodine is present during menstruation pregnancy and infections

Sources of Iodine—Iodine content of food is extremely variable Garden vegetables and legumes contain more iodine than cereals and fruits Sea foods such as oysters lobsters sardines and other fish are rich in iodine The iodine content of milk eggs and vegetables varies with the iodine content of the soil and water of each geographic area In mountain regions, where the water supply is from glacial strata drinking water contains an insufficient amount of iodine The soil is iodine poor Animals and humans become goitrous The administration of sodium iodide twice yearly is sufficient to prevent iodine deficiency This may be supplied by the addition of iodine to drinking water and table salt

Metabolism of Iodine—Iodine is rapidly absorbed from the intestine irrespective of the form in which it is administered It may also be absorbed from the skin and mucous membranes After absorption iodine needed for thyroxin formation is abstracted from the blood stream The excess is distributed to the tissues and excreted Most is eliminated in the urine as inorganic iodide Small amounts appear in milk sweat saliva tears The anterior lobe of the hypophysis produces a thyrotropic hormone which causes an increase of iodine in the plasma by mobilizing it from the thyroid gland

Iodide in Diagnostic Roentgenography—Organic iodide furnishes a contrast medium in diagnostic roentgenography The iodide may be injected directly into a body cavity such as the urinary bladder a nasal sinus or the bronchi Water soluble solutions may be given intravenously for excretory urography (p 2252)

For diagnostic purposes a number of official preparations are recognized These include *lipiodol N N R* (40 per cent iodine) for instillation into the bronchi for visualization of the bronchial tree *lipiodol N.N R* (10 per cent iodine) for injection into the spinal canal for myelography *lipiodine N.N.R* (41 per cent iodine) for contrast roentgenography *diodrast N.N.R* *neoiopax N N R* *hippuran N N R* and *skiodan N.N.R* are water soluble, iodine containing compounds injected intravenously for excretion urography

Iodide as an Expectorant—Iodides are excreted by the bronchial mucous membranes and may be employed as *expectorants* The danger of iodism makes their administration less attractive for this purpose than the use of the ammonium salts

Iodides and Syphilis—Before the modern era in the chemotherapy of syphilis neglected luetic infections went on to the stage of gumma formation The effect of iodides on gummatas is dramatic The swelling becomes smaller and may almost completely disappear under observation It was for this reason that iodide became the miracle drug of the early seventeenth, eighteenth and nineteenth centuries Its use was recommended for

C is not stored beyond the physiologic needs the excess being excreted into the urine (Figs 111 112)

Vitamin C deficiency may be estimated by urinary excretion test or by a chemical determination of the blood level Less than 0 5 to 0 75 mg per 100 c c of reduced vitamin C indicates subnormal intake The capillary resistance test may occasionally reveal the presence of subclinical *scurvy*

Vitamin C Deficiency—It is unlikely that vitamin C deficiency produces any significant clinical manifestations beyond the syndrome of *scurvy* (p 1120) At the time the patient becomes clinically scorbutic there may be other symptoms such as weakness mental depression and digestive disturbances but these are obscured by the bleeding diathesis

Therapeutics—The average daily requirements of vitamin C are 50 mg for the infant and 100 to 150 mg for adults

Vitamin C should be administered in large doses in infant and adult *scurvy* and also in such infections as *pulmonary tuberculosis rheumatic fever* and *whooping cough* in which there may be an increased vitamin C requirement *Peptic ulcer hyperthyroidism pregnancy* and *lactation* also raise the vitamin C requirements In the presence of hemorrhagic states for which no adequate explanation can be found vitamin C should always be administered since it may prove to be a valuable measure

Preparations—There are various ascorbic acid preparations on the market These may be taken orally or administered parenterally On the whole it is more economical to administer the vitamin in the form of food than to administer the synthetic preparations When because of vomiting parenteral administration becomes necessary the synthetic preparations are invaluable *Ascorbic acid U S P* is available in tablet form or as powdered crystals in ampoules suitable for solution and intravenous or intramuscular injection The international unit for vitamin C is the antiscorbutic activity of 0 05 mg of ascorbic acid

Vitamin E (Alpha Tocopherol)

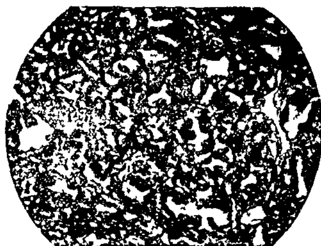
Vitamin E also known as the reproductive and antisterility vitamin is fat soluble Its activity is identical with the synthetically prepared alpha tocopherol There is as yet no estimation of the average daily requirement for the normal individual nor has there yet been expressed a vitamin unit of potency Pure alpha tocopherol is supplied for oral and intramuscular administration in unitages of 50 mg The normal food sources that are rich in vitamin E include wheat germ fresh lettuce leaf whole grain cereal corn olive cottonseed and palm oil

Vitamin E or alpha tocopherol has been employed in the treatment of habitual and threatened *abortion* in threatened *abruptio placentae* in the treatment of the *muscular dystrophies* and in obscure neurological disorders including *amyotrophic lateral sclerosis* Certainly at the present time there are no clear cut evidences of therapeutic effects The original enthusiasm of early experimenters has not been substantiated (p 1509)

Biotin

Biotin is a growth promoting factor that has been isolated and synthesized It is *identical with vitamin H the anti egg white injury factor a*

part to the presence of adenomas Those who subscribe to these views regard goiter prophylaxis as a hazardous venture However acute Graves disease *occurs in any population, goitrous or not* and whether or not iodide prophylaxis has been instituted The onset of an acute episode during the administration of iodide for the prophylaxis of goiter is not necessarily the result of therapy It is more likely coincidental since Graves disease is no



A



B

Fig 101—*A* Microscopical appearance of the gland in exophthalmic goiter showing hypertrophy and hyperplasia (parenchymatous goiter) before the administration of iodine *B* Appearance after involution had occurred from iodine administration (colloid goiter)

more common in the *goitrous and does not occur disproportionately* during goiter prophylaxis (p 1218)

Communities or individual physicians must not be deterred through fear of Jod Basedow s disease from prescribing and sanctioning the use of iodide for the prevention *of endemic goiter*

* After Rienhoff from Best and Taylor Physiological Basis of Medical P Williams & Wilkins Co

jaundice bile salts should also be given to enable the vitamin to be absorbed One or 2 mg of menadione dissolved in sesame or corn oil may be injected subcutaneously or intramuscularly if absorption is inadequate

VITAMIN P (CITRIN)

Vitamin P is a mixture of *hesperidin* and *eriodictyol glucoside* This substance which may be separated from vitamin C (ascorbic acid) controls the permeability of the capillary wall

Vitamin P occurs normally in lemon juice and red peppers It may be used in patients with scurvy who *fail* to respond to the administration of vitamin C alone In nonscorbutic instances attempts have been made to clarify the indications for the administration of vitamin P to individuals possessing capillary fragility as the result of an allergy The vitamin is administered as *calcium eriodictate* and favorable responses have been recorded

UNKNOWN VITAMIN FACTORS

In addition to the vitamins clearly recognized at the present time there are other factors whose usefulness is merely suggested These include *a factor U* which seems necessary for the normal development of the chick *factor W* for rats and dogs *factors R and S* also required by the chick *vitamins L_1 and L_2* required for lactation in the rat *vitamin J* a guinea pig factor *vitamin M* a requirement for the monkey *a chick anemia factor* a *fish anemia factor* and *folic acid* required by micro organisms which apparently also suffer from avitaminosis

MULTIVITAMIN PREPARATIONS

Preparations containing several or all of the available vitamins furnish the single justification for shot gun therapy Often in our present state of knowledge it is better therapeutics and greater economy to prescribe the crude and impure product rather than a synthetic pure preparation This is well illustrated in vitamin B therapy where the whole moiety may be expected to do more than any of its constituents

For multivitamin therapy the Council on Pharmacy has approved preparations containing the approximate daily requirement in each product For therapy these amounts are increased to thiamine 10 mg niacin 50 mg riboflavin 5 mg and ascorbic acid 75 mg taken 2 or 3 times daily as indicated

Therapeutics.—*The most apt summary of vitamin therapy has been* given by Ruffin (Nutrition Rev *2* 353 1944)

1 Vitamin therapy is definitely indicated in patients having objective evidence of a deficiency state but should always supplement dietary treatment never replace it
2 Vitamin therapy is useful in preventing the development of secondary deficiencies in chronic wasting diseases and pre and post operative medical care
3 In the absence of organic disease the individual who consumes a diet adequate in *calories consisting of fruits milk eggs a variety* of meats and green vegetables does not need additional vitamins

adenomas He suggested that there was a qualitative difference in the responses From his views, it was necessary to deduce that iodide was contraindicated in patients with discrete nodules or adenomas Plummer's hypotheses have not been borne out by clinical observation The favorable and unfavorable responses to iodide in the treatment of Graves' disease are equally distributed in the groups with diffuse hyperplasia and those with discrete adenomas It is our viewpoint that the differences in clinical response are wholly quantitative This opinion is discussed in greater detail in the consideration of hyperthyroidism (p 1197)

It is perhaps sufficient to state in this place that those who follow the teachings of Plummer will administer iodides only to those patients who have a diffuse hyperplasia They will regard the drug as contraindicated when there is a discrete nodule or adenoma Those who believe as we do that the changes in response are wholly quantitative must administer iodide to every patient who is threatened with or suffering from anatomical *enlargement of the thyroid gland diffuse or nodular with or without manifestations* of hyperthyroidism The drug is given preoperatively for the relief of the presenting symptoms and the prevention of exacerbation It is given postoperatively and during convalescence in order to prevent a *compensatory hyperplasia of the thyroid remnant and to control symptoms* of hyperthyroidism that may persist or recur during convalescence

Iodine and Iodide Preparations—The official preparations of iodine are the 7 per cent and the 3.5 per cent *tinctures* used almost exclusively for external application

The most popularly used iodide preparation is the *compound solution of iodine* (Lugol's solution) which contains 5 per cent iodine and 10 per cent potassium iodide The effective dose of Lugol's solution may be as little as 0 2 cc or as much as 3 cc daily

The *syrup of hydriodic acid* is somewhat more palatable than the Lugol's solution *Saturated potassium iodide* is the least expensive but the saltiest of the preparations It may be disguised by administration in milk or soup

The Toxicology of the Iodides (Iodism).—Iodide poisoning or iodism is a very frequent clinical phenomenon It may occur as an idiosyncrasy to small dosage or as a cumulative effect after prolonged administration

The symptoms of iodism simulate the ordinary head cold There is stuffiness of the nose irritation of the eyes sneezing increased salivation and an unpleasant taste in the mouth The gums and teeth may be sore The increased amount of bronchial mucus may give rise to a productive cough The superficial lymph nodes and the parotid glands may be swollen Most common are the dermatoses These are commonly small papules resembling acne but may be variegated even appearing like the purpuras

A low grade fever commonly accompanies iodism There are frequent gastro intestinal symptoms particularly nausea vomiting and diarrhea

The frequent occurrence of iodism is a deterrent to the use of the drug When it is employed the patient is warned to report the occurrence of any fresh symptomatology If the physician is in doubt concerning the pathogenesis of the symptoms it is well to discontinue the iodide for several days to observe the effect of withdrawal of the drug upon the newer disturbances

CHAPTER 30

METABOLISM THE AMERICAN DIET

Essential Constituents of the American Diet
- Water
- Milk
- Butter
- Eggs
- Meat, Fish and Poultry
- Grains
- Vegetables
- Fruits
- Nuts
- Fats
- Condiments
- Desserts and Candy
- Carbonated Drinks
- Alcoholic Drinks
- Coffee Tea and Cocoa

Methods of Preparing and Preserving Food

ESSENTIAL CONSTITUENTS OF THE AMERICAN DIET (THE PHARMACOPEIA OF NUTRITION)

THE body requires a constant supply of food materials to furnish energy requirement and to provide for growth and replacement of tissue The substances utilized to satisfy the metabolic needs of the body constitute the *Pharmacopeia of Nutrition*

WATER

Water is an essential constituent of all protoplasm It makes up approximately two thirds of the entire body weight 75 to 90 per cent of the active tissues and 45 per cent of bone

Sources of Supply —The body water is replenished by the *ingestion of liquids or moist foods* (water soups beverages) and by the water that is formed through the *oxidation of hydrogen* Relative to the latter the ordinary mixed diet furnishes daily from 300 to 500 cc of water (about 14 cc per 100 calories) The metabolism of 100 gm of starch yields 55 cc of water of 100 gm of fat 107 cc of water of 100 gm of protein 41 cc of water and of 100 cc of alcohol 117 cc of water

The amount of ingested water varies with diverse circumstances It should be so regulated particularly during illness that the urinary output is brought *to a minimum of 1500 to 2500 cc daily*

MILK

Milk is an important and almost complete food It is the best source of calcium In infant feeding it forms the basis of the diet It is an essential food for the infant and growing child the adolescent and the pregnant woman

Clinical Avitaminoses—Clinical examples of avitaminosis are more difficult of recognition than those produced in the 'pure experiment The patient rarely has only a single deficiency and the syndrome of the avitaminosis is often superimposed upon some profound organic or metabolic disorder As in other situations in clinical medicine the practitioner must often take refuge in the therapeutic test under this circumstance he

TABLE 59—THE COMMONER VITAMINS

Letter	Chemical Name	Physiological Name
A		Antixerophthalmic anti infective
B_1	Thiamine	Antineuritic
B (G)	Riboflavin	
	Nicotinic acid nicotinamide niacin	Pellagra preventive
B_6	Pyridoxine	
	Pantothenic acid	Anti gray hair
C	Ascorbic acid	Antiscorbutic
D	Irradiated ergosterol	Anti rachitic
E	Alpha tocopherol	Fertility antisterility
K	Menadione	Antihemorrhagic

feeds or injects the available vitamins and then draws his conclusions as to diagnosis after he has observed the results of the remedial therapy

The Factors Responsible for Vitamin Deficiencies

Dietary Deficiency (daily requirements are not met)

Decreased Absorption from the Gastro Intestinal Tract
- Abnormalities of the intestinal mucosa
- Lack of digestive enzymes
- Changes in motility (vomiting and diarrhea)
- Altered bacterial flora
- Effect of orally administered medication

Increased Utilization by the Body
- Fever
- Growth
- Pregnancy and lactation
- Increased metabolic rate (hyperthyroidism exercise leukemia and polycythemia)

Increased Elimination from the Body
- Vomiting and diarrhea
- Intestinal fistulas
- Ascitic and pleural fluids
- Vigorous diuresis

Failure of Intermediary Metabolism and Storage

Caloric Value of Milk.—Milk yields approximately 20 calories to the ounce or 635 calories to the quart (946 cc) Each glass of milk furnishes 150 calories The removal of cream from milk reduces its caloric value about one third without impairing its value as a source of protein calcium and phosphorus Skimming lowers the contents of vitamins A and D which are present for the most part in milk fat

Digestion of Milk —Milk is easily digested and absorbed There is no residue to be excreted via the intestinal tract This characteristic gives milk great value as a constituent of bland low residue diets (p 668)

Methods of Preparing Milk for Consumption —Milk is an ideal agent for the transmission of bacteria Milk borne epidemics of typhoid were formerly frequent glandular tuberculosis undulant fever scarlet fever and streptococcus sore throat often owe their dissemination to the use of infected milk.

These hazards have been avoided by the following means

1 *Inspection* of cows barns and milkers for enforcement of standards of cleanliness
2 *Careful handling* of milk after its collection so that its temperature may be kept low before and after pasteurization
3 *Testing of cows* for the presence of tuberculosis mastitis and brucellosis
4 Frequent *bacteriological examination* of the milk.
5 *Pasteurization*

Milk Preparations —A great variety of milk preparations have been made available The advantages of some of these are concerned with the handling and preservation of the product others present modifications designed for some specific therapeutic purpose

Canned Milk Products —Dried whole milk evaporated and condensed milks are sold in cans They may be preserved for an indefinite length of time The bacterial counts are low *These products are highly to be recommended*

DRIED WHOLE MILK POWDER —Dried whole milk powder requires only the addition of water that has been previously extracted This gives a product that is similar to whole milk except that the curd has been rendered more digestible by the heat necessarily applied during the desiccation process

EVAPORATED MILK —Evaporated milk has had one half to two fifths of the water removed by heating The preparation is homogenized The fat is made considerably more digestible by the treatment The restoration of water to make the original volume gives a product that *is similar to whole milk* Evaporated milk like dried whole milk is sterile and is exceedingly useful in infant feeding

CONDENSED MILK —Condensed milk is similar to evaporated milk except that it contains an additional 16 per cent of cane sugar The added sugar prevents the product from freezing and acts as a bacteriostatic Condensed milk is too high in carbohydrate content for infant feeding It is mainly used in beverages with coffee or in cooking processes

MODIFIED MILKS FOR INFANT FEEDING (see also p 2751) —Modified milks for infant feeding are also sold in cans These products are highly



Fig 102 —Follicular hyperkeratosis of vitamin A deficiency





Fig 103 —Hemorrhagic jaundice of vitamin K deficiency

Fig 104 —Rickets due to vitamin D deficiency



Fig 105 —Pitting edema of legs (wet beri beri) and peripheral neuritis of vitamin B deficiency

Courtesy of Eli Lilly and Co

mented milk particularly since the cost is considerably more than that of sweet milk

BUTTERMILK.—*Buttermilk is defatted whole milk containing 3.5 per cent* of protein 4 6 per cent of carbohydrate and but 0.5 per cent of fat It is of great value in the low calory diet (p 669) particularly useful for pur poses of weight reduction

ACIDOPHILUS MILK.—Acidophilus milk differs from fermented milk in that it is essentially a milk culture of the *Lactobacillus acidophilus* The living bacteria are seeded in the intestinal tract for the purpose of altering the bacterial flora of the stool Those who enthusiastically advocate the use of acidophilus believe that the change in flora relieves certain types of constipation (p 1852) and protects the patient from intoxications (p 1821) resulting from the absorption of the products of the other bacterial inhab itants of the intestinal tract particularly *B coli* and *S faecalis* While the clinical results are not consistent an occasional striking result justifies clinical trials

Other Milk Products JUNKET.—Junket is coagulated milk protein pre cipitated out of milk when junket tablets have been added It may be flavored and served as a simple dessert in infant feeding or in the dietary of the convalescent or the invalid

CHEESE.—Cheese represents one other medium for the ingestion of milk Brands of cheese vary greatly *Soft cream cheese* is made from sour or sweet cream thickened with rennet

Soft cheese is easily digested An average portion may yield from 300 to 500 calories *Cottage cheese* prepared from skimmed milk is used in low calory diets since one hundred grams of cottage cheese give but 100 cal ories against a 400 calory yield from a similar portion of cream cheese or Swiss cheese

The *rancid cheeses* of the Camembert type have a rind of moulds Limburger cheese owes its powerful odor and taste to products of putre factive bacteria

Whatever the form of cheese it is a highly nutritious food rich in pro tein fat and minerals

ICE CREAM.—Ice cream is a palatable method of feeding milk Plain ice cream contains 13 per cent of fat The richer ice creams may run as high as 23 per cent of fat The protein content is 3½ per cent and the carbo hydrate approaches 20 per cent Ice cream regarded as a luxury and used as a treat for children is actually more highly nutritious and digestible than many of the alleged necessities such as spinach

BUTTER

Butter contains the *fat* of the milk in semisolid form A good dairy butter yields approximately 90 per cent of fat and significant amounts of vitamin A with smaller amounts of vitamin D Salt is usually added to freshly churned butter to retard the deterioration Unsalted butter or so called sweet butter apparently keeps equally well and many prefer its use

Butter a good source of vitamin A is not superior in vitamin content to butter substitutes made from animal oils and neutral lard

Butter being pure fat yields 9 calories per gram Butter substitutes

Official Pharmaceutical Preparations Dosage and Daily Requirements.—The official commercial preparations are prepared from fish liver oil or solutions of pure carotene

Carotene N.N R supplies vitamin A without D It is dissolved in cotton seed oil in the concentration of 7500 units per gram

The U S P preparations of cod liver oil include the pure *cod liver oil U.S.P* and *nondestearinated cod liver oil U S P These preparations contain* at least 850 units of vitamin A per gram

Cod liver oil is the cheapest source of vitamin A but its fishy taste and large volume required make it unpleasant to take These difficulties have been partially overcome by concentration by the addition of flavoring and by emulsification with other substances

The N N R preparations include *cod liver oil concentrate halibut liver oil percomorph liver oil burbot liver oil* and *shark liver oil*

The cod liver oil *concentrates* contain 1400 units of vitamin A per gram as a minimum and a proportionate amount of vitamin D

Halibut liver oil preparations must contain a minimum of 44 800 units of vitamin A per gram and are relatively deficient in vitamin D

Percomorph liver oil yields 60 000 units of vitamin A per gram as well as large amounts of vitamin D and constitutes the richest source for these vitamins It is the preparation of choice

Burbot and shark liver oils contain much smaller quantities of both vitamins

VITAMIN D

A large variety of chemical substances possess vitamin D activity All have in common the fact that they are derived from *cyclopentenophenanthrene*

The Natural Sources of Vitamin D.—Vitamin D occurs richly in the normal dietary in cod liver egg yolk herring irradiated foods particularly milk salmon sardines and many of the shell foods such as crabs clams scallops and shrimp

The Daily Requirement of Vitamin D.—The normal adult requires a small dosage of vitamin D perhaps less than 400 units daily During pregnancy and lactation the intake should be increased to 800 units daily Infants and growing children require 400 to 800 units in twenty four hours

Absorption Fate and Excretion of Vitamin D.—Vitamin D is readily absorbed through the gastro intestinal tract when an adequate amount of bile is present Approximately 25 per cent of the orally ingested vitamin D escapes in the feces even under normal conditions

Vitamin D may be slightly stored in all tissues It is relatively stable and is not destroyed for a considerable time Excretion occurs through the milk and probably through the feces Thus vitamin D given to a nursing mother, results in milk with considerable antirachitic potency

Physiological Functions of Vitamin D.—Vitamin D is concerned with the intestinal absorption of calcium and phosphorus It may also function to convert organic phosphate to the inorganic form particularly in bone Parathyroid extract also functions in calcium and phosphorus metabolism but its effect is to increase the urinary excretion of phosphate thus lower

have an identical caloric value and may be used interchangeably The caloric value of a diet may be easily increased by the liberal use of butter

Butter Substitutes —Butter substitutes are recommended as an economy measure They are usually *vegetable margarines* with added salt vitamins A and D The fat content and caloric yield equal those of pure butter and the digestibility is the same The Council on Foods of the American Medical Association has approved several brands

Butter substitutes of vegetable origin are also valuable as a low-cholesterol fat in some metabolic disorders

EGGS

The egg is an important constituent of the American dietary It is usually the important course in the breakfast menu particularly in rural districts and may also form the main course of the evening meal Hens eggs are usually employed In some neighborhoods duck eggs are substituted

Chemical Composition.—The average egg will yield 75 calories of fuel value The *white of the egg* contains approximately 12 per cent protein the rest being virtually all water The *yolk* contains 50 per cent water approximately 35 per cent fat and the remainder is protein

The *protein* of the eggs is of the highest quality The *fat* is finely emulsified and easily assimilated Vitamins A B and D are present in eggs

Digestibility.—The digestibility of the egg is excellent The hard boiled grated egg is most easily digested Contrary to general opinion the raw egg may be poorly digested the protein passing unchanged into the stool

Utilization of Eggs.—In the normal American diet eggs may appear as such or they may be utilized in the preparation of sauces cake custard etc

While the egg is an economical food on the farm it is a luxury food in the city districts because of the difficulties of handling

It is well to include at least one preferably two eggs daily in the diet of the child and adolescent The adult should consume at least six eggs a week and preferably ten or a dozen if the budget and the appetite permit

MEAT FISH AND POULTRY

Meat fish and poultry constitute with milk and eggs the main sources of protein in the American diet

The protein foods commonly form the principal course of the principal meal whether this meal be eaten in the middle of the day as in rural neighborhoods or in the evening as in the cities The accessory meal oftentimes is built upon a principal course of protein food using cold meat warmed left-overs hash or chopped meat (hamburger)

The Composition of Meat —The generic term meat is used to include muscle meats of pig cow lamb chicken turkey duck goose game birds rabbit and deer animal organs such as liver kidney stomach (tripe) pancreas heart brain and testicle (lamb fry) fish and shellfood Meat is a relatively expensive luxury in the dietary Every effort should be made to provide a liberal portion at least three times a week and preferably once daily

That excessive consumption of meat is a factor in the development of

Calcium is mobilized from bone, and the concentration of calcium in the serum is elevated

Vitamin B Complex

The members of the B group of vitamins are dissimilar in composition and function The best understood at present are thiamine hydrochloride (B_1) riboflavin (B_2 or G) nicotinic acid (pellagra preventive) and choline Others which have recently been isolated are pyridoxine (B_6) para aminobenzoic acid pantothenic acid inositol biotin factor W

Thiamine Hydrochloride (Vitamin B_1)—Thiamine is a complex molecule containing *pyrimidine* and *thiazole* The latter is of particular importance in chemotherapy, as a portion of the sulfathiazole molecule (p 89)

Natural Sources—Vitamin B_1 or thiamine hydrochloride occurs abundantly in bran whole grain, ham and particularly lean pork the dried legumes nuts cheese soy bean yeast, and slightly in green vegetables and fruits The daily requirement approximates 2 mg

Absorption Fate and Excretion—Thiamine is readily absorbed parenterally or enterally and is stored in all of the tissues of the body, particularly the liver brain kidney and heart

Thiamine is largely destroyed in the body Five to ten per cent of the daily intake is excreted in the urine except in cases with marked deficiency

Many clinicians believe that thiamine is poorly absorbed under certain conditions hence the vogue for the intravenous injection of the pure crystalline substance

The Physiology and Pharmacology of Thiamine—Thiamine plays an essential role in the intermediary metabolism of carbohydrate An important step in this process is the conversion of pyruvic acid to acetaldehyde through the mediation of the enzyme carboxylase Since absence or deficiency of thiamine results in diminished utilization of tissue oxygen and accumulation of pyruvic acid it is thought that thiamine functions as a co enzyme (co carboxylase) in this reaction Nervous tissues deriving energy entirely from carbohydrate oxidation are particularly vulnerable to thiamine deficiency

The injection (intravenous) of large amounts of thiamine hydrochloride may give rise to toxic effects such as weakness and dyspnea These symptoms should not result from doses in the therapeutic range The patient rapidly recognizes the yeasty taste of the thiamine and this may be employed as a rough test of circulatory function (p 787) Occasionally there is a transitory sense of fulness and/or cutaneous vasodilatation

Thiamine Deficiency—The early manifestations of thiamine deficiency have been very clearly outlined by the production of the syndrome in human volunteers Within a few weeks most patients note fatigue, lassitude loss of appetite loss of weight insomnia irritability paresthesias of the lower extremities constipation dyspnea edema an initial hyperreflexia followed by hyporeflexia muscle hyperesthesia tachycardia decreased gastric acidity and radiographic evidences of lowered intestinal tone The general syndrome if observed clinically might well be confused with 'neurasthenia (p 1341)

Prolonged or excessive thiamine deficiency produces the syndrome of *beriberi* In the United States this is most often seen in the course of

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Fig 106 —Photophobia epiphora and scleral injection in riboflavin deficiency



Fig 107 —Cheilitis and photophobia in riboflavin deficiency



Fig 108 —Glossitis of niacin deficiency



Fig 109 —Pellagrous dermatitis of niacin deficiency



Fig 110 —Pellagrous dermatitis of hands in niacin deficiency

Courtesy of Eli Lilly and Co

Coo	2 3	0 0	0	1 3	0	0	200	0	0	173	¼ lb	11
Ha ldock	17 2	0 0	0 3	72	7	10	0	0	66	81	¼ lb	113
H l but	18 6	0 0	1 0	121	0	40	0	17	74	137	¼ lb f l t	113
Ham (fat)	14 6	0 3	14 0	1 6	0	180	0	0	100	31	¼ lb	113
H m (lean)	19 5	0 3	25 0									
H rri g	19 0	0 0	8 7	136	200	40	0	1200	150	154	1 fl t	113
Lamb chop	21 7	0 7	29 9	3 9	0	100	0	0	110	406	2 cl ops	113
Lol ter	16 2	0 5	1 9	84	0	50	100	0	32	95	¾ c (canned)	113
Ma garı e	0 6	0 4	81 0	733	6	0	0	0	0	103	1 tablespoonful	14
Mince m at	6 7	60 2	1 4	280	0	0	0	0	0	316	¼ lb	113
M tton leg	19 8	0 0	12 4	191	0	120	50	0	110	216	¼ lb	113
Oysters	9 8	5 9	2 0	81	210	50	60	5	180	92	6	113
Po k chop (good grade)	14 8	0 0	32 0	317	0	150	38	0	100	392	2 chops	113
Pork cl ops (common grade)	17 9	0 0	18 0									
Pork sausage	10 8	0 0	44 8	446	0	150	0	0	100	156	2 links	3
Pabl ıt	20 8	0 0	10 2	175	0	11	80	0	24	198	½ lb	113
Salmon	17 4	0 0	16 5	218	270	40	0	460	80	246	1 c canned	113
S rd nes ın o l	25 7	1 2	11 0	207	400	30	0	1500	250	104	4 sardines	0
Scallop	14 8	3 4	0 1	74	0	0	60	0	0	84	¾ c	113
Sh ımp	2 4	0 2	1 0	111	0	30	50	0	64	5	8	65
Trip	19 1	0 0	2 0	94	0	0	0	0	0	106	¼ lb	113
Tuna ın o l	24 2	0 0	10 8	194	0	0	0	0	0	219	1 c (canned ın o l)	113
Turkey	4 0	0 0	6 7	156	0	0	0	0	0	1 6	¼ lb	113
Veal chops (good grade)	18 6	0 0	15 0	209	0	40	0	0	36	236	2 chops	113
Veal chops (common grade)	19 7	0 0	8 0									
Veal cutlet (good grade)	19 1	0 0	12 0	184	0	40	0	0	120	208	¼ lb	113
Veal cutlet (common grade)	19 9	0 0	6 0									
Whitefi h	22 9	0 0	6 5	150	0	30	0	0	0	170	¼ lb (filet)	11

From brochure o Nutrition published by H J Heinz Company
† Vitamins A B_1 C and D are expres ed ın International Units per 100 gm vitamın B_2 or G ın Sherman Bourquın Units

later the involved skin becomes rough and desquamates following this there may be edema and ulceration

The tegumentary and digestive symptoms are associated with psychiatric abnormalities These may consist of an accentuation of the minor early manifestations or there may be disorientation, hallucination and mania (Figs 108 109 110)

Preparations—*Nicotinic acid U.S.P nicotinic acid amide N N R* and *sodium nicotinate* are the chief preparations in use Of these nicotinic acid is the most popular It is available in 25 50 and 100 mg tablets for oral administration and in the various concentrations in ampoules for parenteral use Nicotinic acid especially when taken on an empty stomach may cause an unpleasant pricking facial erythema This is avoided by using the amide form

Pantothenic Acid—Pantothenic acid is available for general purposes as a *d* calcium pantothenate Pantothenic acid is also known as the filtrate factor, the chick dermatitis factor Rats fed on a diet deficient in pantothenic acid show extensive damage to the kidneys, necrosis and hemorrhages being commonly observed Similar changes have been noted in the adrenal glands Clinically the deficient animal demonstrates poor growth dermatitis and graying of the hair It seems unlikely that pantothenic acid deficiency can occur in subjects on a normal diet since there are so many easily available food sources for the substance These include

	Percentage
Fair Sources	
Whole milk	0.1
Buttermilk	0.5
Kale	0.3
Squash Italian	0.3
Artichokes Jerusalem	0.4
Polished rice	0.4
Carrots	0.2
Tomatoes	0.1
Good Sources	
Sweet potatoes	1.1
Rolled oats	1.1
Wheat	1.1
Rye	1.0
Rye flour dark	1.3
Rye middlings	2.3
Barley	1.0
Broccoli	1.1
English walnuts	0.8
Yellow corn	0.8
Irish potatoes	0.7
Taro root	0.7
Excellent Sources	
Brewer s yeast, dry	20.0
Liver	4.0
Egg yolk	6.3
Peanuts	5.3
Eggs	2.7
Split peas	2.1

TABLE 37.—COMPOSITION OF CEREALS

Name	Percentage of weight			Calories per 100 grams	Vitamin content†					Average portion		
	Protein	Carbohydrate other than fiber	Fat		A	B_1	C	D	B or G	Total calories	Measure	Weight grams
Barley, pearled	8.2	8.3	1.0	355	0	17	0	0	4	107	3 tablespoonfuls	30
Bread, rye	8.9	49.2	2.0	250	0	38	0	0	0	125	3 slices	50
Bread, white	8.5	52.0	2.0	260	0	30	0	0	26	130	2 slices	50
Bread, whole wheat	9.5	47.0	3.5	258	10	120	0	0	41	129	2 slices	50
Cornmeal, yellow	9.1	71.0	3.7	357	420	78	0	0	32	107	3 tablespoonfuls	30
Farina	11.5	77.8	1.0	358	0	17	0	0	0	107	3 tablespoonfuls	30
Flour, buckwheat	6.3	79.3	1.1	352	0	0	0	0	0	77	2 tablespoonfuls	22
Flour, rye	8.9	77.4	0.9	353	0	57	0	0	24	64	2 tablespoonfuls	18
Flour, soybean	37.3	9.5	20.2	379	0	0	0	0	0	68	2 tablespoonfuls	18
Flour, white	10.8	75.6	0.9	354	0	29	0	0	16	60	2 tablespoonfuls	17
Hominy	8.5	78.5	0.8	355	0	60	0	0	0	178	¼ cup	50
Macaroni or spaghetti	13.0	3.5	1.4	359	0	43	0	0	0	101	¼ cup	28
Oatmeal	14.2	67.0	7.4	391	0	270	0	0	83	98	¼ cup	25
Rice, white	7.6	79.2	0.3	350	0	7	0	0	32	98	2 tablespoonfuls	28
Tapioca	0.6	86.3	0.[illegible]	349	0	0	0	0	40	140	¼ cup	40
Wheat bran	16.0	50.2	5.2	312	0	200	0	0	110	87	1 cup	28
Wheat germ	25.2	47.0	10.0	379	420	1100	0	0	300	76	2 tablespoonfuls	20
Wheat, whole	11.7	74.0	2.0	361	14	170	0	0	80	72	2 tablespoonfuls	20

From brochure on Nutrition published by *H. J. Heinz Company.*
† Vitamins A, B_1, C and D are expressed in International Units per 100 gm; vitamin B_2 in Sherman Bourquin Units.



Fig 111 —Gingivitis of scurvy in vitamin C deficiency Angular scarring of lips from associated riboflavin deficiency

Fig 112 —Capillary hemorrhages in adult scurvy due to vitamin C deficiency

Courtesy of Eli Lilly and Co

and constitute fairly good sources of protein Vitamins B_1 and B_2 are present in small amounts and the iron content is relatively high

Cooking legumes with baking soda to make them bright green though esthetically desirable is nutritionally unsound since a good deal of the vitamin B content is thereby destroyed

Roots and Tubers —*Potatoes carrots beets turnips* and *radishes* are the commonest roots and tubers Potatoes contain abundant carbohydrate (20 per cent) a good quality protein and considerable minerals Sweet *potato* has similar nutritional characteristics and an additional 5 per cent of sugar thiamin and riboflavin Carrots are a good source of vitamin A and when eaten raw yield some vitamin C The beet provides sugar its leaves contain vitamins A and B_2 Turnip contains vitamin A and some vitamin C Its leaves are also good sources of vitamins A and riboflavin

Stems and Bulbs—*Celery* and *asparagus* are popular salad vegetables *Onion* when raw yields appreciable amounts of vitamin C The *tomato* is a valuable source of vitamins A B_1 B and C The vitamin C content is retained even after canning

Caloric Values of Vegetables —It is convenient to classify vegetables according to their caloric values or the percentage value of available carbohydrates A useful classification recognizes the existence of 5 10 and 15 per cent vegetables In the following table 100 gm (approximately ½ cup) contains the designated percentage of carbohydrate (4 calories per gm)

TABLE 38 —CLASSIFICATION OF VEGETABLES

5 per cent	*10 per cent*	*15 per cent*
Asparagus (fresh and canned)	Artichokes (French)	Artichokes (Jerusalem)
Beans	Beets	Corn (canned)
Broccoli	Brussels sprouts	Parsnips
Cabbage	Carrots	Potatoes
Cauliflower	Lima beans	Succotash (canned)
Celery	Onions	
Cucumbers	Peas	
Lettuce		
Radishes		
Spinach		
Squash		
Tomatoes		

The physical form of vegetables is important in dietetics They provide undigested residue which has a high satiety value in low calory dietaries

FRUITS

Besides being pleasant to the taste the fruits furnish a variety of important nutritional elements The *apple* contains appreciable amounts of sugar and very small amounts of vitamins A B and C It also contains pectin Its laxative property probably depends on its cellulose Fresh and canned *citrus fruits* are good sources of vitamin C Oranges contain a good deal of dextrose and are therefore useful where a readily assimilable sugar is needed Citrus fruits produce alkaline ash despite their acid flavor

Pears peaches apricots cherries plums prunes and *berries* share the above properties to greater or smaller extent In addition apricots peaches prunes and raisins are good sources of iron and may be used as adjuvants to medicinal hematinics The *banana* finds use in the dietary of young children as an easily digestible source of vitamins A C and B_2 and carbo

substance which prevents a dermatitis that characteristically occurs when egg white is used as a source of protein in the feeding of rats The role of biotin in human nutrition has not yet been determined

VITAMIN K

One of the greatest hazards of surgery in jaundiced patients has always been their tendency to uncontrollable bleeding Recently, this has been shown to be the result of *prothrombin* deficiency which can be repaired by the administration of vitamin K

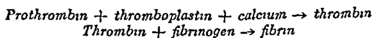
Source Absorption and Physiology—Vitamin K is widely distributed in green leaves being especially plentiful in spinach alfalfa cabbage group and soy beans It also occurs in putrefied fish meal and is synthesized by intestinal bacteria

Nothing is known of the normal human minimal requirements

Natural vitamin K being fat soluble is absorbed only in the presence of *bile salts* Synthetic water soluble derivatives probably require no bile salts for absorption

Vitamin K aids in the formation of prothrombin probably in the liver since hepatectomized animals fail to show change in clotting time after administration of the vitamin In the presence of liver degeneration (whether experimentally produced or in clinical conditions such as cirrhosis or acute yellow atrophy) no improvement in prothrombin time or hemorrhagic tendency follows vitamin K medication

Measurement of Prothrombin Deficiency—Prothrombin deficiency is measured by the so called "prothrombin time test The patient s oxalated plasma is recalcified with calcium chloride Thromboplastin in the form of rabbit s brain is added and the time for clotting to occur is measured and compared with a control plasma run simultaneously The clotting mechanism depends on reactions which are indicated by the following equations



Prothrombin + thromboplastin + calcium → thrombin
Thrombin + fibrinogen → fibrin

If the prothrombin content of blood is low clotting will be delayed only because of its lack since all other elements of the reaction have been supplied (Fig 103)

Vitamin K Deficiency—The clinical deficiencies of vitamin K in the newborn or the adult are manifest essentially by the hemorrhagic diathesis associated with hypoprothrombinemia These are discussed in greater detail in the Section on the Diseases of the Blood (p 1111)

Therapeutics—Vitamin K is indicated prophylactically in all patients with obstructive jaundice before and after operation even in the absence of hypoprothrombinemia

The vitamin should be used to prevent and to treat *hemorrhagic disease of the newborn* (p 1111) due to neonatal prothrombin deficiency The administration of the substance to the mother in the last week of pregnancy prevents the disease by assuring an adequate prothrombin level in the blood of the newborn

Preparations—Menadione (2 methyl naphthoquinone) U.S.P is a synthetic compound having the physiological properties of vitamin K It may be given orally in doses of 1 to 2 mg daily In cases o bstructive

Ca l c	4.4	19.0	9	0	0	270	0	0	0	1 l ve peeled	2
Hor erad sh	3.2	19.0	91	0	0	1800	0	0	9	1 tabl spoon ful	10
K le	3.9	6.0	45	37 000	63	2900	0	190	45	1 cup leaves	100
Kohl abi	2.1	5.6	32	0	10	1000	0	0	32	½ cup	100
Lambsq arters	3.8	5.7	44	*19 000*	0	0	0	0	44	1 cup leaves	100
Leeks	2.5	6.6	40	2	40	470	0	0	23	2 bulbs	57
Lentils dried	4.7	56.6	334	200	120	0	0	27	94	2 tablespoonfuls	28
Lettuce	1.2	2.3	16	2 200	29	250	0	40	12	¼ head	75
Marrow vegetable	0.5	3.4	17	30	15	220	0	0	17	½ cup	100
Mushrooms	0	0	0	0	50	35	0	0	0	7	100
Mustard greens	2.3	3.2	25	440	46	3500	0	150	25	1 cup leaves	100
Okra	1.8	6.4	35	840	42	340	0	0	17	5 pods	50
Onions	1.4	9.5	45	0	11	190	0	11	23	1	50
Parsley	3.7	7.2	53	5 000	0	2800	0	0	0	1 sprig	1
Parsnips	1.5	16.0	75	200	38	800	0	0	75	½ large	100
Peas dried	23.8	54.8	327	5 100	120	0	0	120	92	2 tablespoonfuls	28
Peas green	6.7	15.5	92	2 000	130	500	0	100	92	¾ c shelled	100
Peppers green	1.2	4.3	24	1 100	6	3600	0	72	24	1 empty pod	100
Potatoes sweet	1.8	26.9	121	4 200	35	650	0	34	175	1 pared	145
Potatoes white	2.0	18.7	84	56	40	560	0	46	101	1 pared	120
Pumpkins	1.2	6.0	31	9 200	18	190	0	18	31	½ cup seeded rind removed	100
Radishes	1.2	3.5	20	0	30	520	0	8	7	5	100
Rhubarb	0.5	3.1	15	650	0	300	0	0	15	1 cup stems	100
Rutabagas	1.1	7.6	36	25	25	600	0	40	36	½ cup	100
Salsify (oyster plant)	3.5	13.7	78	0	0	140	0	0	78	2 scraped	100
Sauerkraut	1.3	3.5	21	20	8	0–190	0	0	21	½ cup	100
Spinach	2.3	2.6	22	8 400	35	860	0	80	22	1 cup leaves	100
Squash summer	0.6	3.4	17	2 100	14	460	0	6	16	1 cup seeded	100
Squash winter	1.5	7.4	38	7 000	16	0	0	18	38	1 cup seeded	100
Taro	2.0	20.7	93	0	0	0	0	0	93	1 corm pared	100
Tomatoes	1.0	3.4	20	2 000	26	510	0	36	20	1 small cored	100
Turnips	1.1	6.0	30	15	20	600	0	30	30	½ cup pared	100
Turnip greens	2.9	4.2	32	11 000	45	2600	0	300	32	1 cup leaves	100
Watercress	1.7	2.8	21	1 400	45	1200	0	90	21	2½ cup leaves	100
Watermelon ‡											
Yams	2.1	23.3	103	88	0	120	0	0	155	1 tuber pared	150
Yautia yellow	2.2	24.9	110	100	27	0	0	0	110	1 corm pared	100

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† Vitamins A B_1 C and D are expressed in International Units per 100 gm vitamins B_2 or G in Sherman Bourquin Units
‡ See Table 40 under Melons

4 Vague symptoms such as weakness fatigability insomnia nervousness and irritability are more apt to be due to overwork nervous tension or to social domestic or financial difficulties than to a vitamin deficiency

5 For the most part prolonged vitamin therapy in the absence of obvious disease is useless"

A more realistic viewpoint of the present scene is that of Carlson (Lancet *43* 371 1943) who says The public has been rendered vitamin conscious by the press radio and by the less critical laboratory and clinical workers in nutrition The detail man is eloquent and persuasive So lest we over look a bet we join the vitamin bandwagon

Pears	0 7	13 4	0 4	64	15	19	100	0	60	64	2 halves cored	100
Persimmons	0 8	32 0	0 4	135	180	0	3 0	0	0	13	1 small seeded	100
Pineapples	0 4	13 3	0 2	57	100	25	3 0	0	23	57	2 slice canned	100
Plums	0 7	12 4	0 2	54	150	40	100	0	18	54	3 stoned	100
Prunes dried	2 5	60 4	0 6	202	1300	60	0	0	260	202	4 stewed stoned	100
Quinces	0 3	12 1	0 1	51	0	0	170	0	0	51	1 boiled as sauce	45
Raisins	2 3	69 5	0 5	202	84	24	0	0	30	131	¼ c seeded	100
Raspberries black	1 5	12 1	1 6	69	0	0	600	0	0	69	½ cup	100
Raspberries red	1 1	11 6	0 6	56	260	30	600	0	0	0	½ cup	100
Strawberries	0 8	6 9	0 6	38	120	11	1200	0	120	56	12 hulled	100
Tangerines	0 8	9 9	0 3	46	300	40	900	0	16	40	2 peeled seeded	100

From brochure on Nutrition published by H J Heinz Company

† Vitamins A B C and D are expressed in International Units per 100 gm vitamin B_2 or G in Sherman Bourquin Units

TABLE 40A —CARBOHYDRATE CLASSIFICATION OF FRUITS

5 per cent	*10 per cent*	*15 per cent*	*18 per cent*	*High Carbohydrate*
Rhubarb, canned	Applesauce canned un sweetened	Apples fresh	Cherries sweet, fresh	Apples dried
Cantaloupe	Apricots canned	Blueberries fresh	Crab apples, fresh	Apricots dried
Gooseberries canned	Blackberries fresh and canned	Cherries, black	Figs fresh	Bananas fresh or dried
Melons honeydew	Blueberries canned	Grapes fresh	Persimmons	Cherries (maraschino) canned
Peaches canned	Cherries red and white	Huckleberries fresh	Prunes canned	Figs dried
Plums (not prunes) canned	Cranberries	Oranges, fresh		Fruits canned in syrup (all kinds)
Strawberries fresh and canned	Gooseberries fresh	Pears fresh		Peaches dried
	Grapefruit fresh	Pineapple canned		Prunes canned or dried

Since the American dietary is often deficient in calcium the adult should drink daily one pint of milk

Chemical Composition of Milk —Milk contains more of the nutritive essentials than any other single food

TABLE 34 —AVERAGE COMPOSITION OF COW AND HUMAN MILK

	Cow	*Human*
Water	87.5 per cent	87 6 per cent
Lactose	5.0	7.5
Fat	4 0	3.5
Protein	3 4	1.25
Ash	0 7	0.2
Calcium	0 12	0 03
Phosphorus	0.09	0.012
Iron	0 0002	0 0002

Protein —Due to the abundance of essential amino acids milk proteins (*casein* and *lactalbumin*) are of high biologic value A quart of milk contains enough protein to supply the daily protein requirement of a child under 3 and one third of the protein needed by an older child

Fat.—The fat of milk is highly emulsified and easily digested The fat globules coalesce as the milk stands forming a layer of cream at the top of the bottle In cream milk fat averages from 16 to 18 per cent, though it may be as high as 60 per cent

Carbohydrate —The principal carbohydrate of milk is *lactose* a readily available sugar It is believed to enhance the absorption of calcium from the intestine

Minerals —The mineral content of milk is a characteristic of great value Milk is the richest source of *calcium* furnishing 1 2 gm to the quart It is also a valuable source of *phosphorus* (0 9 gm to the quart) A quart of milk daily furnishes the calcium and phosphorus requirement for the child a pint supplies the requirement of the average adult During pregnancy it is impossible to meet the calcium requirement from dietary sources unless adequate amounts of milk are consumed

A notable deficiency in milk is its low *iron* content Milk anemia' is observed in infants fed exclusively on human or cow s milk This deficit is remedied by the early inclusion of other foods in the infant diet

Vitamins —Milk is an excellent source of some of the vitamins Depending on the feed of the cow a quart of milk supplies from 1000 to 2000 U.S P units of *vitamin A* (one third to two thirds of the minimum requirement for older children and adults) Yellow milks contain large amounts of carotene and small amounts of vitamin A Milks of lighter color contain more vitamin A and less carotene The proportion of vitamin A to carotene varies with different breeds of cows

The *vitamin D content* of milk varies with the season During the winter milk contains 5 to 10 U S P units per quart against 15 to 40 units during the summer This amount is negligible in comparison to the daily human requirement and has led to the fortification of milk with vitamin D

Milk contains only a small portion of the thiamine needed by infants older children and adults but the riboflavin content approximates the estimated adult need The vitamin B content is small and after pasteurization it is even further reduced

TABLE 41.—COMPOSITION OF NUTS

Name	Percentage by weight			Calories per 100 grams	Vitamin content†					Total calories	Average portion	
	Protein	Carbohydrate other than fiber	Fat		A	B_1	C	D	B_2 or G		Measure	Weight grams
Almonds	18.6	16.9	54.1	629	0	100	0	0	0	88	12 nuts	14
Brazil nuts	14.4	8.9	65.9	686	0	340	0	0	0	96	2 nuts	14
Butternuts	23.7	8.4	61.2	679	0	0	0	0	0	95	4 nuts	14
Cashews	19.6	25.4	47.2	605	0	0	0	0	76	85	10 nuts	14
Chestnuts, fresh	2.8	40.4	1.5	180	0	50	0	0	0	26	3 nuts, skinless	14
Coconut, dried	6.3	28.1	57.4	654	0	24	0	0	42	92	2 tablespoonfuls	14
Hazelnuts (filberts)	12.7	14.3	60.9	6 6	0	150	0	0	0	92	10 nuts	14
Hickory	13.9	11.0	67.4	706	0	0	0	0	0	99	12 nuts	14
Peanuts	26.9	21.2	44.2	590	26	220	0	0	200	83	16 nuts, skinless	14
Pecans	9.4	10.8	73.0	738	330	100	0	0	100	103	12 meats	14
Pistachio	19.6	16.4	53.2	623	200	0	0	0	0	87	⅓ cup	14
Walnuts, black	18.3	16.8	58.2	664	0	0	0	0	0	93	12 meats	14
Walnuts, English	15.0	13.5	64.4	694	830	130	0	0	0	97	12 meats	14

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† Vitamins A, B_1, C and D are expressed in International Units per 100 gm; vitamin B_2 or G in Sherman Bourquin Units.

recommended because of their convenience stability bacteriological and chemical attributes, and their relatively lower costs Included in the milk modifications accepted by the Council on Foods of the American Medical Association are S.M.A and Similac

S M A is a skimmed cow s milk fortified by the addition of a potassium salt and sufficient lactose to approach the composition of human milk A mixture of cod liver oil with vegetable and animal fat has been homogenized and incorporated to the proportion of 4 per cent or the equivalent of the fat content of cow s milk The cod liver oil also furnishes an abundance of vitamins A and D Easily assimilable iron and thiamine chloride have been added to fulfil all nutritional requirements

Three and one half tablespoons of S M.A is the equivalent of one ounce yielding 140 calories The standard solution is readily prepared by diluting one tablespoonful with 2 ounces of water The simplicity of this method of infant feeding recommends itself to the practitioner and mother alike

Bottled Milk Products HOMOGENIZED MILK —Homogenized milk has been forced under pressure through fine apertures As a result the fat globules have become smaller and remain uniformly suspended throughout the milk A layer of supernatant cream does not form upon standing The fats and curd are rendered more digestible by homogenization

PEPTONIZED MILK —Peptonized milk is prepared by adding sodium bicarbonate and pancreatic ferment to a mixture of milk and water The result is a partially digested product which may be of limited value in infant feeding and the management of individuals with allergy

PROTEIN MILK —Protein milk is a coagulated milk protein with added buttermilk It contains very little fat It is prepared by adding tablets of junket or pepsin to whole milk The curd is separated from the whey after straining through cheesecloth Buttermilk is then added Protein milk is of value in the treatment of the infantile diarrheas (p 2782) Dried protein milk may be purchased in cans

ACIDIFIED MILK (Lactic Acid Milk) —Acidified milk has been treated with lactic or citric acid The curd is thus made finer Lactic acid milk is employed in infant feeding especially in the treatment of vomiting It is available in powdered form sold in cans

VITAMIN D MILK —Milk with its high content of calcium and phosphorus is an excellent and very logical carrier of added vitamin D Vitamin D milks include fresh pasteurized milk dried whole and skimmed milks evaporated milk and flavored whole or skimmed milk

Vitamin D may be added to milk directly from natural or manufactured vitamin D concentrates by feeding of vitamin D preparations to cows or by the irradiation of milk Milks with a vitamin D content ranging from 135 to 400 U S P units to the quart or reconstituted quart have been accepted by the Council on Foods of the American Medical Association These milks when fed in adequate quantity will prevent clinical rickets

FERMENTED MILK —Fermented milk enjoys a large popularity The various brands are Koumyss Zoolak Matzoon and Yoghurt They possess no metabolic or nutritional superiority to sweet milk Additional claims as to their therapeutic value particularly with regard to longevity are myths The best excuse for their ingestion is their palatability for those who enjoy their taste There seems to be no other reason for prescribing fer

TABLE 43.—FAT CONTENT OF COMMON FOODS

Low fat content (less than 2 %)	Medium fat content (2 to 10%)	High fat content (above 10%)
Vegetables	Cream soup	Butter (fat and oils)
Fruits	Milk	Salmon
Cereals	Veal	Tunafish
Bread	Chicken	Lamb
Egg white	Turkey	Pork
Buttermilk	Lean beef	Duck
	Crab meat	Egg yolk

CONDIMENTS

Salt is the only common flavoring substance which has essential metabolic value A minimum of 2 gm a day added to food should be sufficient for the average adult Salt is important in maintaining fluid balance Its absence or loss often leads to asthenia and disturbances in electrolyte balance

Vinegar (acetic acid) *spices* (usually containing volatile oils) and *flavoring extracts* (alcoholic solutions of plant principles) find use as flavoring adjuvants but have little or no food value

TABLE 44.—COMPOSITION OF CONDIMENTS*

Variety	Percentage by weight			*Total calories per 100 grams*
	Carbohydrates other than fiber	*Protein*	Fat	
57 Beefsteak sauce	16 7	2 2	2 1	87
Chili sauce	26 0	2 5	0 7	120
Chow chow	2 5	1 6	1 4	29
Horse radish (evaporated)	66 8	15 6	0 9	338
India relish	28 0	0 5	0 3	117
Mayonnaise dressing* (see note)	1 3	1 4	82 3	754
Mustard (brown)	5 2	5 2	7 5	109
Mustard (yellow)	9 1	4 7	4 6	97
Sandwich spread	17 0	0 3	36 8	401
Sour onions	1 0	0 2	trace	5
Sweet onions	37 0	0 1	trace	148
Dill pickles	0 5	0 8	0 3	8
Fresh cucumber pickle	15 9	1 2	0 2	70
Sour pickles	1 3	0 9	0 2	11
Sweet pickles	34 0	0 7	0 2	141
Sweet mustard pickle	25 3	1 4	0 4	110
Tomato ketchup	25 0	2 5	0 2	.06
Olive oil			100 0	903
Ripe olives	2 9	1 2	21 0	206

From brochure on Nutrition published by H J Heinz Company
e = eggs

DESSERTS AND CANDIES

The satiety value of a meal is incomplete without dessert This attribute of the dessert depends on its sugar and fat which retard gastric emptying

Because of their high caloric value desserts are at once the nemesis of the obese and the medicine of the undernourished Much has been said of their indigestibility but careful preparation renders pie crust and fried cakes assimilable by all but the most intolerant

Candies are made of sucrose and glucose with chocolate and other flavoring They are of value chiefly for their sugar content They may in sufficient quantities retard gastric evacuation

TABLE 35 — COMPOSITION OF DAIRY PRODUCTS*

Name	Protein	Carbohydrate	Fat	Calories per 100 grams	Vitamin content†					Average portion		
					A	B_1	C	D	B_2 or G	Total calories	Measure	Weight grams
Butter	0 6	0 4	81 0	733	3800	0–30	0	100	0	103	1 tablespoonful	14
Buttermilk	3 5	5 0	0 2	36	0	0	0	0	62	80	1 glass	240
Cheese American	23 9	1 7	32 3	393	3400	14	0	33	170	110	1 slice	28
Cheese Cheddar	22 3	1 7	30 2	368	3400	14	0	33	200	103	1 cube	28
Cheese cottage	19 2	4 3	0 8	101	110	0	0	0	x	58	¼ cup	37
Cheese Roquefort	21 7	1 4	33 2	391	4000	10	0	x	x	109	1 slice	28
Cheese Swiss	28 6	1 9	31 3	404	2000	x	0	x	150	113	1 slice	28
Cream sour	2 5	4 5	18 5	195	2200	21	0	50	xx	29	1 tablespoonful	15
Cream sweet	2 9	4 0	20 0	208	1000	10	0	50	xx	31	1 tablespoonful	15
Ice cream	3 9	20 3	13 0	214	900	8	0	x	20	214	½ cup	100
Milk condensed	8 1	54 8	8 4	327	680	32	20	0	140	98	2 tablespoonfuls	30
Milk dried	35 6	52 0	1 0	359	0	110	0	0	640	80	4 tablespoonfuls	24
Milk evaporated	7 0	9 9	7 9	139	500	19	30	m	130	160	½ glass	115
Milk goat	3 3	4 8	4 2	70	170	10	30	5	33	168	1 glass	240
Milk human	1 4	7 2	3 7	68	350	10	120	0	25	68		100
Milk skim	3 5	5 0	0 2	36	0	13	27	0	65	80	1 glass	240
Milk whole (pasteurized)	3 5	4 9	3 9	69	240	12	14	0	62	160	1 glass	240
Whey dried	13 0	74 5	0 5	355	x	x	0	0	1200			

* From brochure on Nutrition published by H J Heinz Company

† Vitamins A B_1 C and D are expressed in International Units per 100 gm vitamin B_2 or G in Sherman Bourquin Units

TABLE 46.—ALCOHOLIC BEVERAGES

Beverage	Portion	Quantity	Alcohol per cent by weight	Total fuel value in calories
Distilled Liquors				
Brandy California	Cordial glass	20 cc	45 80	65
Brandy cherry		20	44 00	62
Brandy cognac, pure French		20	55 90	78
Cocktail, dry Martini	Cocktail glass	75	21 30	131
Gin		50	30 00	116
Liqueurs				
Benedictine	Cordial glass	20	42 40	88
Chartreuse		20	35 20	78
Curaçao		20	42 00	82
Crême de menthe		20	36 50	4
Kümmel		20	26 00	61
Rum		50	43 50	153
Rum pure Jamaica		50	69 61	245
Whiskey American, genuine		50	43 00	152
Whiskey European		50	39 00	137
Wines and Ciders				
1 American Wines				
California red	Claret glass	120	9 50	95
California white		120	9 00	89
Sweet wines				
Catawba	Sherry glass	30	11 07	30
Champagne	Champagne glass	135	8 27	132
Port California	Sherry glass	30	14 81	53
Sherry California		30	14 67	38
2 European Wines				
Champagne dry	Champagne glass	13	10 42	112
French red (claret)	Claret glass	120	8 16	81
French white		120	9 48	95
Mosel and Saar white		120	7 36	73
Rhein white		120	8 12	83
Sweet wines				
Champagne	Champagne glass	135	9 50	161
Madeira	Sherry glass	30	15 40	39
Malaga		30	11 93	52
Marsala		30	15 85	40
Port		30	16 69	45
Sherry		30	17 45	42
Tokay fresh		30	11 19	39
3 Ciders				
American sweet	Glass	250	1 40	109
American fermented		250	5 17	130
Malt Liquors				
1 American				
Ale		2 0	6 02	155
Lager beer bottled		250	4 53	130
Lager beer draft		2 0	4 27	1 0
Porter		2 0	4 46	140
2 European				
Ale		250	5 27	154
Bock beer		250	4 20	146
Export beer		250	4 29	142
Light beer		2 0	3 69	120
Munich heavy beer		2 0	4 54	182
Pilsen export beer		250	4 28	123
Porter (Stout)		250	5 16	172
Weissbier		250	2 79	103

The enormous variation in the composition of alcoholic liquors has made it exceedingly difficult to choose values which should be accurate and comparable As a rule the percentages given are averages of a large number of analyses and if not strictly accurate are as nearly so as it is possible to obtain them

TABLE 56 —COMPOSITION OF MEATS FISH AND POULTRY PRODUCTS
(EDIBLE PORTION)

Name	Percentage by weight			Calories per 100 grams	Vitamin content†					Average portion		
	Protein	Carbo hydrate	Fat		A	B_1	C	D	B_2 or G	Total calories	Measure	Weight grams
Bacon (lean)	12 2	1 1	53 0	531	0	90	0	0	61	149	4 slices	28
Beef brains	10 5	1 4	8 8	127	0	56	370	0	120	144	¼ lb	113
Beef chuck (good grade)	17 6	0 0	22 0	268	21	28	0	0	110	303	¼ lb	113
Beef chuck (common grade)	19 2	0 0	9 0									
Beef corned (medium)	15 8	0 0	25 0	288	0	0	0	0	0	325	¼ lb	113
Beef corned (very lean)	19 4	0 0	8 0									
Beef heart (lean)	16 0	0 7	3 7	104	0	220	84	0	300	118	¼ lb	113
Beef kidney	15 0	0 0	8 1	137	1100	100	210	0	840	155	1 cup	113
Beef liver	19 7	0 0	3 2	132	14000	89	820	50	1000	149	¼ lb	113
Beef loin (good grade)	15 6	0 0	31 0	341	21	28	36	0	110	385	¼ lb	113
Beef loin (common grade)	18 6	0 0	16 0									
Beef steak (good grade)	18 7	1 4	17 0	233	21	30	30	13	110	263	¼ lb	113
Beef steak (common grade)	19 7	0 0	8 0									
Beef sweetbreads (good grade)	10 3	0 0	41 0	410	0	13	0	0	0	463	1 cup	113
Beef sweetbreads (common grade)	14 4	0 0	19 0									
Beef tongue (good grade)	15 7	0 4	18 0	226	0	05	0	0	88	170	5 slices	76
Beef tongue (common grade)	17 4	0 4	11 0									
Bluefish	20 5	0 0	4 0	118	0	0	0	0	0	134	1 filet	115
Bologna	14 4	0 0	17 8	218	0	0	0	0	0	94	4 slices (skin removed)	4
Chicken	21 0	0 0	4 [illegible]	12	0	32	80	0	08	141	¼ lb	11
Clams	12 8	3 4	1 4	77	28	7	000	0	5	87	[illegible]	115
Codfish	16 5	0 0	0 4	70	10	40	0	0	04	70	¼ lb	113
Crabs	16 1	0 6	1 6	81	0	4	250	0	140	92	1 cup	113
Duck	21 4	0 0	8 2	1 9	0	0	150	0	0	180	¼ lb	115
Egg white	10 8	0 8	0 0	46	0	0	0	0	90	16	1 white	35
Egg yolk	16 3	0 7	31 0	355	3 00	120	0	100	200	60	1 yolk	1
Eggs	12 8	0 7	11 [illegible]	1 8	2700	0	0	05	120	82	[illegible]	54
[illegible]	8 6	0 0	0 1	315	0	0	0	0	0	31	[illegible]	[illegible]

Canned foods require less processing in the home Special varieties e g purees and small cut vegetables and meats are useful in infant feeding and in the preparation of soft diets

Canned foods may be obtained in the raw state (vegetables) after cooking (fruits meats etc) dried in powder form (milk etc) and ready to serve (spaghetti soups etc)

Smoking Salting and Drying.—Where adequate transportation and refrigeration facilities are lacking meat may be preserved for considerable periods of time by smoking salting and drying These processes do not greatly impair the nutritive value of the meat although in drying considerable fat is lost

Freezing.—Freezing methods are useful for the preservation of meats fruits and vegetables Frozen meats maintain their nutritive values intact for long periods Vegetables and fruits subjected to quick freezing processes are well preserved if kept at low temperatures in airtight water proof containers There is slight loss of vitamins particularly ascorbic acid but with proper methods of handling these losses may be minimized Frozen foods contain very few bacteria but should be used at once on thawing

TABLE 36.—COMPOSITION OF MEATS, FISH AND POULTRY PRODUCTS
(EDIBLE PORTION)

Name	Percentage by weight			Calories per 100 grams	Vitamin content†					Average portion		
	Protein	Carbohydrate	Fat		A	B_1	C	D	B_2 or G	Total calories	Measure	Weight grams
Bacon (lean)	12.2	1.4	53.0	531	0	90	0	0	61	149	4 slices	28
Beef brains	10.5	1.4	8.8	127	0	56	370	0	120	144	¼ lb	113
Beef chuck (good grade)	17.6	0.0	22.0	268	21	28	0	0	110	303	¼ lb	113
Beef chuck (common grade)	19.2	0.0	9.0									
Beef corned (medium)	15.8	0.0	25.0	288	0	0	0	0	0	32[illegible]	¼ lb	113
Beef corned (very lean)	19.4	0.0	8.0									
Beef heart (lean)	16.9	0.7	3.7	104	0	220	84	0	300	118	¼ lb	113
Beef kidney	15.0	0.9	8.1	137	1100	100	210	0	840	1[illegible]5	1 cup	113
Beef liver	19.7	6.0	3.2	132	14000	89	820	50	1000	149	¼ lb	113
Beef loin (good grade)	15.6	0.0	31.0	341	21	28	36	0	110	38[illegible]	¼ lb	113
Beef loin (common grade)	18.6	0.0	16.0									
Beef steak (good grade)	18.7	1.4	17.0	233	21	30	36	13	110	263	¼ lb	113
Beef steak (common grade)	19.7	0.0	8.0									
Beef sweetbreads (good grade)	10.3	0.0	41.0	410	0	13	0	0	0	463	1 cup	113
Beef sweetbreads (common grade)	14.4	0.0	19.0									
Beef tongue (good grade)	15.7	0.4	18.0	226	0	9[illegible]	0	0	88	170	[illegible] slices	7[illegible]
Beef tongue (common grade)	17.4	0.4	11.0									
Bluefish	20.5	0.0	4.0	118	0	0	0	0	0	133	1 filet	11[illegible]
Bologna	14.4	0.0	17.8	218	0	0	0	0	0	94	4 slices (skin removed)	4[illegible]
Chicken	21.0	0.0	4.[illegible]	125	0	32	80	0	68	141	¼ lb	11[illegible]
Clams	12.8	3.4	1.4	77	28	7	600	6	[illegible]	87	9	113
Codfish	16	0.0	0.4	70	10	40	0	0	64	79	¼ lb	11[illegible]
Crabs	16.1	0.6	1.6	81	0	4	2[illegible]0	0	140	92	¾ cup	113
Duck	21.4	0.0	8.2	159	0	0	1[illegible]0	0	0	180	¼ lb	11[illegible]
Egg white	10.8	0.8	0.0	46	0	0	0	0	90	16	1 white	35
Egg yolk	16.3	0.7	31.9	35[illegible]	3[illegible]00	120	0	300	200	60	1 yolk	1[illegible]
Egg	12.8	0.7	11	1[illegible]8	2700	50	0	95	120	82	1 shell r no 1	5[illegible]
Gelatin dried	8.6	0.0	0.1	343	0	0	0	0	0	31	1 tablespoonful	[illegible]

TABLE 47—RECOMMENDED DIETARY ALLOWANCES

Food and Nutrition Board, National Research Council

	Calories	Protein gm	Calcium gm	Iron mg	Vitamin A I U	Thiamine (B₁) mg	Riboflavin mg	Niacin (nicotinic acid) mg	Ascorbic acid mg	Vitamin D I U
Man (70 kg)										
Sedentary	2500	70	0 8	12	5000	1 5	2 2	15	75	†††
Moderately active	3000					1 8	2 7	18		
Very active	4500					2 3	3 3	23		
Woman (56 kg)										
Sedentary	2100	60	0 8	12	5000	1 2	1 8	12	70	†††
Moderately active	2500					1 5	2 2	15		
Very active	3000					1 8	2 7	18		
Pregnancy (latter half)	2500	85	1 5	15	6000	1 8	2 5	18	100	400 to 800
Lactation	3000	100	2 0	15	8000	2 3	3 0	23	150	400 to 800
Children up to 12 yrs										
Under 1 year†	100/kg	3 to 4/kg	1 0	6	1500	0 4	0 6	4	30	400 to 800
1-3 yrs††	1200	40	1 0	7	2000	0 6	0 9	6	35	†††
4-6 yrs	1600	50	1 0	8	2500	0 8	1 2	8	50	
7-9 yrs	2000	60	1 0	10	3500	1 0	1 5	10	60	
10-12 yrs	2500	70	1 0	12	4500	1 2	1 8	12	75	
Children over 12 yrs										
Girls 13-15 yrs	2800	80	1 3	15	5000	1 4	2 0	14	80	†††
16-20 yrs	2400	75	1 0	15	5000	1 2	1 8	12	80	
Boys 13-15 yrs	3200	85	1 4	15	5000	1 9	2 4	18	90	†††
16-20 yrs	3800	100	1 4	15	6000	2 3	3 0	30	100	

Tentative goal toward which to aim in planning practical dietaries; can be met by a good diet of natural foods. Such a diet will also provide other minerals and vitamins, the requirements for which are less well known.

1 mg thiamine equals 333 I.U.; 1 mg ascorbic acid equals 20 I.U.

Requirements may be less if provided as vitamin A; greater if provided chiefly as the provitamin carotene.

† Needs of infants increase from month to month. The amounts given are for approximately 6-8 months. The amounts of protein and calcium needed are less if derived from human milk.

†† Allowances are based on needs for the middle year in each group (as 2, 5, 8, etc.) and for moderate activity.

††† Vitamin D is undoubtedly necessary for older children and adults. When not available from sunshine, it should be provided probably up to the minimum amounts recommended for infants.

arteriosclerosis and hypertension is one of many food fallacies Eskimos subsisting almost wholly on fish are rarely subject to these diseases Experimental feeding with beef confirms these findings in temperate climates

Muscle Meats—The muscle meats vary as to the amount of fat, the proportion being particularly great in pork muscle Variations in the chemical composition also depend upon the *cut of the meat* The fat content is least in the butt end and highest in the lower loin region from which club steaks are commonly cut In addition to proteins and fat muscle contains extractives such as *creatine* and the *purine bases* The vitamin content of all meat is low except for considerable amounts of thiamine and niacin especially in lean pork muscle

Animal Organs—Animal organs furnish a more complete food than muscle meat They have an appreciable amount of vitamin A thiamine niacin and riboflavin Liver and kidney are rich in the anti anemic principle (p 1081) a specific in the treatment of pernicious anemia

Meat Extracts—Meat extracts erroneously believed to be highly nutritious are virtually without food value Meat broths and beef tea carefully exclude all the nutritive elements

Fish and Poultry—Fish and poultry do not differ materially in composition from meat but fish is poor in riboflavin and in thiamine The idea that protein derived from fish or poultry is lighter or more easily digestible than red meat is without foundation

Canned fish and dried fish are quite as nutritious as fresh fish The fish livers furnish a large supply of vitamins A and D

Shellfish—Shellfish particularly oysters clams crabs lobster and shrimp are widely eaten as accessory or luxury foods They are rich in iodine and calcium and vitamin D Oysters and clams fattened in brackish or contaminated water and eaten in toto including the intestinal tract and its contents can certainly appeal only to those who know not what they do' Crabmeat lobster meat and shrimp so commonly cause enteritis and are so frequently involved in allergic idiosyncrasy that the normal dietary would suffer little by their complete exclusion

Meat Handling—Meat is commonly preserved in cold storage by canning smoking or freezing Properly prepared canned and frozen meats are both palatable and nutritious

Inspection of meat rigidly carried out by the United States Department of Agriculture constitutes one of the great services of the Federal government Among the many diseases transmitted through infected carcasses are trichinosis tularemia brucellosis and tapeworm infestation

Grains (Cereals)

The *grains* furnish the bulk of the world s food supply *American wheat* is the grain most widely used *Rye* and *barley maize* and *oats* are next in importance *Rice* although the most important food in the Oriental countries is relatively sparingly consumed in America

Roughly the food value of an ounce of milled grain yields approximately 100 calories

Carbohydrate—The *carbohydrate* of the grain is its chief nutritive constituent Man s carbohydrate the world over comes from this source to a large degree or from potatoes or rice (Russia Germany Ireland)

Vitamin Need—The noncalorigenic essentials include the vitamins and the minerals

The daily vitamin requirement of the normal adult approximates 5000 international units of *vitamin A* or 2.5 mg of beta carotene supplied by 5 gm of cod liver oil of *vitamin B_1* 400 international units or approximately 1 8 mg of thiamine hydrochloride supplied by 9 gm of dried yeast of *riboflavin* 600 Sherman units or about 3 mg of the pure substance of *nicotinic acid* 18 mg of *vitamin C* 1000 international units or 75 mg of ascorbic acid as furnished by 100 cc of orange juice of *vitamin D* 500 international units or 12 micrograms of calciferol

The vitamin requirement of the pregnant or lactating woman exceeds that of the normal adult (p 2629)

Mineral Need—The daily mineral requirement of the average adult includes 10 gm of salt 3 gm of potassium 1.3 gm of phosphorus 1 gm of calcium 15 mg of iron 3 mg of copper 1.5 mg of manganese and 0 1 mg of iodine

Of the minerals iron is apt to be deficient in infants and children who are fed a diet exclusively of milk Iodine may be deficient in the mountainous regions where the water supply emanates from a glacial stratum (goiter belt) and calcium is notoriously absent from the American dietary due to an insufficient ingestion of milk and dairy products

Daily Food Intake—Translated into the simple terms of the food served on the American table the metabolic needs may be obtained from the following substances

Cow s milk one pint for the adult one quart for infant or child
Eggs one or two daily or navy beans
Meat fish or poultry one serving daily or at least four servings a week
Potato one daily
Cooked vegetables two cooked vegetables daily one of which should be green or yellow preferably prepared in a pressure cooker to preserve the mineral and vitamin content
Raw vegetable one serving daily
Fruits one or more servings daily either raw or cooked
Butter or *oleomargarine*

The remainder of the diet may be selected according to taste but should include *cereal bread fat* and a reasonable amount of *sweets*

The whole grain cereals and bread are preferred for their increased mineral vitamin and roughage content

Daily Meals—The distribution of the basic dietary needs in the conventional three daily meals may be approximated in the following manner The choice of foods is made with a view to low cost

BREAKFAST

Raw cooked, fresh or dried *fruit*
Cereal with *milk* or *cream*, and *suga*
One or two eggs or *navy beans*
B ead or toast with *butter* or *oleomargarine*
A glass of *milk*
A *beverage* such as coffee or tea

Proteins and Vitamins—The *proteins* of grain are of fair quality *Vitamin A* is present in only small amounts *Vitamin B* which is contained in whole grain is removed almost entirely in the process of milling and preparing the white flour that is most popularly used Enriched breads are white breads to which vitamin B has been added

Whole wheat bread retains a great part of the vitamin B complex Whole grain also contains vitamin E and a certain amount of B but no C The cellulose of the wheat kernel of whole wheat bread is of value as a bulky stimulant to peristalsis

There is very little difference between the grains of barley buckwheat flour corn meal rice rye or wheat flours

The grains are commonly eaten as *bread* or the *table cereals* Bread may be made in loaves in small rolls in biscuits muffins or crackers

Bread—Bread is a nutritious food and a relatively cheap source of calories Since it contains from 8 to 12 per cent *protein* the consumption of one quarter of a pound of bread daily furnishes one tenth of the adult protein requirement Bread protein is of high biological value and is well utilized

The *vitamin content* of bread varies with the type of flour from which it is made Removal of the wheat germ and the bran in the process of milling wheat flour reduces the vitamin B content of white bread to 15 per cent of the amount of vitamin present in whole grain The *war breads* have all been fortified with vitamins and contain a rich yield of both B and D

The *mineral content* of bread depends on whether or not milk is used in its preparation Breads containing milk are good sources of calcium

Bread furnishes about 1200 calories per pound or 75 calories per ounce The carbohydrate value of any diet may be raised or lowered by varying the number of slices of bread allowed Bread has a high satiety value Its carbohydrate is liberated more slowly than other more available sources of glucose

Cake has the same nutritive value as bread Pastry contains added fat and is often less digestible

Cereals—Cereals may be cooked or served cold just as they come from the package One of the main advantages of breakfast food is the necessity for adding milk or cream and sugar

VEGETABLES

Leafy Vegetables—The common leafy vegetables in the dietary are *cabbage cauliflower lettuce broccoli spinach* and the *greens* of *beets* and *turnips* They constitute an important source of minerals roughage and vitamins—chiefly A, B_2 C and K Vitamin C is largely destroyed in the process of cooking

Vitamins and minerals are best preserved by serving vegetables with the water in which they are cooked or by pressure cooking Though spinach is an excellent source of vitamins A and K it is no better than its less widely publicized sisters No justifications exist for the practice of forcing large quantities of this food down the throats of unwilling children who may prefer other vegetables

Legumes—*Beans* and *peas* are the most popular legumes in America

The construction of the diet must always take into account the normal dietary habits and the individual idiosyncrasy of the given patient It is for this reason that routine diet lists are to be condemned The individual dietary can only be intelligently and successfully prescribed after inquiry and investigation

The Diet During Pregnancy

The gravid woman requires dietary supplements particularly in the latter half of pregnancy The average woman gains approximately 15 pounds during pregnancy Her *caloric intake* builds up to 2500 to 3000 calories per day The additional *protein* and *calcium* are best supplied by increasing the milk intake to 1 quart daily supplemented where possible by milk products such as cheese custard buttermilk ice cream The increased *vitamin* requirement necessitates at least twice the amounts taken ordinarily Increased amounts of *iron* are necessary to prevent nutritional anemia and for fetal requirements The maternal *calcium* depots must be kept replenished both for maintenance of the structural integrity of the mother and for proper nutrition of the fetal osseous system Increased amounts of *iodine* must also be administered to prevent the goiter of pregnancy In the event that there is doubt concerning the mineral or vitamin content of the diet in pregnancy it is justifiable to supplement the food stores by the administration of iron calcium iodine and vitamins in concentrated pill form

The requirements during pregnancy may be summarized as follows

Total Calories (for a woman weighing 123 pounds)	2500
Protein	85 gm
Calcium	1.5 gm
Iron	15 mg
Vitamin A	6000 I U
Thiamine	1.8 mg
Riboflavin	2.5 mg
Nicotinic Acid	18 mg
Ascorbic Acid	100 mg
Vitamin D	400–800 I U

The Diet During Lactation

The diet during lactation does not differ appreciably from the diet in the latter months of pregnancy It is important to maintain a relatively high *protein* intake approximately 100 to 125 gm daily This is best obtained from milk eggs and the meat products The *minerals* particularly *calcium* and the *vitamins* must be supplied exactly as during pregnancy

The dietary should contain for a moderately active woman weighing 123 pounds

Total Calories	3000
Protein	100 gm
Calcium	2 gm
Iron	12–15 mg
Vitamin A	8000 I U
Thiamine	2 3 mg
Riboflavin	3 0 mg
Nicotinic acid	23 mg
Ascorbic acid	150 mg
Vitamin D	400–800 I U

TABLE 39 —COMPOSITION OF VEGETABLES

Name	Percentage by weight		Calories per 100 grams	Vitamin content†					Total calories	Average portion	
	Protein	Carbo hydrate other than fiber		A	B_1	C	D	B_2 or G		Measure	Weight grams
Artichokes (globe)	2 9	8 7	50	390	50	220	0	0	50	1 heart edible leaf portion	100
Asparagus	2 2	3 2	23	1 400	45	800	0	55	23	6 stalks	100
Bamboo shoots	2 5	4 3	30	22	18	110	0	0	30	¾ cup	100
Beans baked	6 0	17 8	99	75	40	0	0	0	99	½ cup	100
Beans dried	22 0	58 2	334	110	110	0	0	95	190	¼ cup shelled	57
Beans green	2 4	6 3	37	1 100	25	430	0	60	37	1 cup (stringless)	100
Beans dried lima	20 7	57 3	324	0	130	0	0	100	91	⅛ cup	28
Beans green lima	7 5	22 0	125	900	87	840	0	100	125	⅔ cup shelled	100
Beets	1 6	8 7	42	50	5	160	0	11	42	⅔ cup	100
Beet greens	2 0	4 2	28	21 000	37	720	0	250	28	1 cup	100
Broccoli	3 3	4 2	32	17 000	30	1300	0	160	32	1 cup curd	100
Brussels sprouts	4 4	7 6	53	400	60	3000	0	0	53	6	100
Cabbage	1 4	4 3	25	38	28	2000	0	25	14	¾ cup (shredded)	57
Cantaloupe‡											
Carrots	1 2	8 2	40	7 700	23	75	0	30	40	1 large	100
Cauliflower	2 4	4 0	27	70	56	730	0	32	27	1 cup curd	100
Celeriac (celery root)	1 7	7 4	39	0	0	0	0	0	39	¼ cup	100
Celery	1 3	3 0	19	35	10	170	0	17	8	2 stalks	40
Chard leaves	2 6	4 0	30	24 000	150	170	0	55	30	1⅓ cup	100
Collards	3 9	6 0	45	6 200	53	1400	0	100	45	⅔ cup	100
Corn canned	2 5	19 2	95	0	50	100	0	0	109	½ cup	115
Corn green (yellow)	3 7	19 7	104	560	50	850	0	40	104	½ cup cut (from cob)	100
Cucumbers	0 7	2 2	13	35	30	200	0	0	7	10 slices	57
Dandelion greens	2 7	7 0	45	33 000	0	750	0	0	45	1 cup	100
Eggplant	1 1	4 6	25	70	20	120	0	26	25	2 1	100
Endive	1 6	3 2	21	970	26	2 0	0	24	9	⅓ h ad	4
Escarole (chickory)	1 6	2 1	18	23 000	2	140	0	94	3	½ h d	16

TYPE MEALS

BREAKFAST

One portion dry cereal
One egg
Bread or *toast* with butter
One teaspoonful sugar
One half glass water coffee milk buttermilk or fruit juice

10 A.M.

One half glass water milk, buttermilk, fruit juice or soup without salt

DINNER

Meat.
Potato (baked)
Vegetable
Raw carrot, celery or lettuce
Cookie or cake without icing
Bread and butter
1 teaspoonful sugar
One half glass fluid

3 P.M.

One half glass fluid, consisting of water coffee buttermilk, or fruit juice

SUPPER OR LUNCHEON

Cheese or egg dish
Potato or macaroni or rice
Vegetable.
Fruit.
Bread and butter
1 teaspoonful sugar
One half glass of fluid (water coffee, buttermilk, or fruit juice)

THE LIQUID DIET

Indications—For *postoperative psychotic* or *unconscious* patients the caloric intake may be maintained with fluid nourishment given in small frequent feedings either by mouth or through an indwelling gastric tube Liquid mixtures are also suitable for gastrostomy feedings

A minimum of 360 cc of fresh fruit or vegetable juice per day must be included to insure adequate vitamin and mineral intake

Tube Feeding Formula—McLester suggests the following tube feeding formula (1100 cc = 1900 calories)

100 gm strained oatmeal
300 cc milk
300 cc 18 per cent cream
40 gm vitavose (a maltose dextrin preparation)
60 cc orange juice
50 gm dextrose
30 gm butter or olive oil
1 teaspoonful salt

DIET—*Approximately* 2500 calories (carbohydrate 350 gm protein 87 gm fat 88 gm) are provided by the following liquid diet administered in twelve portions given every two hours

1 One half cup thick gruel composed of barley arrow root farina cream of wheat or wheatena plus one half cup milk and one tablespoon sugar

TABLE 40 —COMPOSITION OF FRUITS

Name	Percentage by weight			Calories per 100 grams	Vitamin content†					Total calories	Average portion	
	Protein	Carbo-hydrate other than fiber	Fat		A	B_1	C	D	B_2 or G		Measure	Weight gram
Apples	0 3	13 9	0 4	60	110	4	120	0	1[illegible]	120	1 large cored	200
Apricots	1 0	12 3	0 1	54	8000	9	60	0	42	54	4 halves stoned	100
Avocados	2 0	4 0	17 2	179	6[illegible]0	20	60	0	[illegible]	179	½ pear stoned	100
Bananas	1 2	2[illegible] 4	0 2	96	320	20	[illegible]60	0	35	96	1 small peeled	100
Blackberries	1 2	7 8	1 1	46	400	13	75	0	0	46	1 cup	100
Blueberries (huckleberries)	0 8	13 9	0 6	63	100	15	170	0	7	63	⅔ cup	100
Cherries	1 1	14 5	0 5	67	700	17	2 0	0	0	67	18 stoned	100
Cranberries	0 4	9 9	0 7	48	28	0	220	0	0	48	1 cup	100
Currants	1 6	9 5	0 4	48	400	10	410	0	0	48	1 cup	100
Dates dried	2 2	73 0	0 6	306	210	20	0	0	0	92	4 stoned	30
Figs dried	4 0	62 6	1 2	277	45	24	0	0	40	83	1½	30
Gooseberries	0 8	7 6	0 4	37	1 0	50	420	0	0	37	¾ cup	100
Grapefruit	0 [illegible]	9 8	0 2	43	0	24	820	0	40	43	½ cup juice	100
Grapes	1 4	14 4	1 4	76	50	6	110	0	0	76	1 bunch seeded	100
Guavas	1 0	11 6	0 6	[illegible]	200	14	2,[illegible]00	0	3[illegible]	56	1 pared seeded	100
Lemons	0 9	7 8	0 6	40	0	18	910	0	0	40	½ cup juice	100
Limes	0 8	8 6	0 1	39	130	0	720	0	0	39	½ cup juice	100
Loganberries	1 0	13 6	0 6	64	0	11	690	0	0	64	1 cup	100
Mangoes	0 7	16 2	0 2	69	3,[illegible]00	21	530	0	98	69	½ pared seeded	100
elons												
Cantaloupes	0 6	4 0	0 2	20	590	10	[illegible]0	0	30	40	½ seeded rindless	200
Honeydew	0 6	7 5	0 2	34	0	0	1800	0	0	68	½ seeded rindless	200
Muskmelons	0 6	5 4	0 2	26	590	19	500	0	30	52	½ seeded rindless	200
Watermelons	0 5	6 3	0 2	29	120	9	150	0	14	58	1 slice seeded	200
ectarines	0 5	15 6	0 1	6[illegible]	2800	0	500	0	0	6[illegible]	2 pared stoned	100
ives green	1 5	2 8	13 [illegible]	130	300	0	0	0	0	33	[illegible] small stoned	25
ranges	0 9	10 6	0 2	48	90	26	960	0	25	48	½ cup juice	100
apayas	0 6	11 1	0 1	40	3000	6	840	0	33	40	½ seeded	100
eaches	0 [illegible]	11 4	0 1	49	980	6	200	0	18	49	1 large pared	100

TYPE MEALS

BREAKFAST

One portion dry cereal
One egg
Bread or *toast* with butter
One teaspoonful sugar
One half glass water coffee, milk, buttermilk or fruit juice.

10 A.M

One half glass water milk, buttermilk, fruit juice or soup without salt

DINNER

Meat.
Potato (baked)
Vegetable
Raw carrot, celery or lettuce
Cookie or cake without icing
Bread and butter
1 teaspoonful sugar
One half glass fluid

3 P.M.

One half glass fluid, consisting of water coffee buttermilk, or fruit juice

SUPPER OR LUNCHEON

Cheese or egg dish
Potato or macaroni or rice
Vegetable.
Fruit.
Bread and butter
1 teaspoonful sugar
One half glass of fluid (water coffee, buttermilk, or fruit juice)

THE LIQUID DIET

Indications —For *postoperative psychotic* or *unconscious* patients the caloric intake may be maintained with fluid nourishment given in small frequent feedings either by mouth or through an indwelling gastric tube Liquid mixtures are also suitable for gastrostomy feedings

A minimum of 360 cc of fresh fruit or vegetable juice per day must be included to insure adequate vitamin and mineral intake

Tube Feeding Formula —McLester suggests the following tube feeding formula (1100 cc = 1900 calories)

100 gm strained oatmeal
300 cc milk
360 cc 18 per cent cream
40 gm vitavose (a maltose dextrin preparation)
60 cc orange juice
50 gm dextrose
30 gm butter or olive oil
1 teaspoonful salt

DIET —*Approximately* 2500 calories (carbohydrate 350 gm protein 87 gm fat 88 gm) are provided by the following liquid diet administered in twelve portions given every two hours

1 One half cup thick gruel composed of barley arrow root farina cream of wheat or wheatena plus one half cup milk and one tablespoon sugar

hydrate Its carbohydrate is most easily assimilated when the fruit is thoroughly ripened

Apple powder and *banana powder* are available in cans These desiccated preparations are useful in dietotherapy—the former in the management of diarrhea and dysentery the latter for general metabolic conditions particularly those characterized by milk idiosyncrasy and fat intolerance Apple powder yields 96 calories to the ounce A 5 per cent aqueous mixture flows through the nipple of the ordinary nursing bottle Banana powder alters the intestinal flora from gram negative to gram positive It dissolves readily in milk and water retains the carbohydrate food value and natural vitamins (A B_1 B_2 B_6 and C) Three tablespoonfuls are somewhat less than an ounce (100 calories) and more than the equivalent of an average banana The greatest use for banana powder is in the treatment of celiac disease (p 1937)

Nuts

The nutritive value of nuts depends chiefly on the high fat and protein content and moderate amounts of vitamin B Except for chestnuts nuts have a low carbohydrate content

Soups and Broths

Soups are extensively employed as the first course of the two principal meals in the forcing of fluids and as a tentative feeding for an intolerant stomach

The clear soups such as broths consomme and bouillon have little nutritive value Compared to the effort that is often employed in their preparation they represent a maximum culinary effort with a minimum metabolic result They serve to enlarge a low calory meal (p 669) and are useful as fillers

A certain amount of nutritive value may be obtained from clear soups if vegetables the starches (such as noodles) or bread are added

The thicker or so called creamed soups are prepared with flour they may have a considerable caloric value and are useful in the high calory diet (p 671)

Canned soups are of high quality and palatability

Fats

Fats provide one third of the caloric requirements of the body *Butter cream* and *fish oils* are rich also in vitamin

Butter Substitutes—In addition to the dairy products butter substitutes are commonly used *Oleomargarine* represents a mixture of oleo oil lard milk cream and butter *Lard* used chiefly in cooking is refined pork fat *Cottonseed oil* substitutes are said to be superior to lard

Vegetable Oils—Various types of oils have a limited use as food *Olive oil* though pleasant to taste has no particular advantage over the other edible vegetable oils *Peanut and corn oils* are occasionally used as inexpensive substitutes for olive oil

Meat Fat—The main sources of meat fat are *bacon* and *pork* and especially cuts of meat above the butt Duck is especially fat Lamb tunafish and salmon are rich in fat

Vegetable Fat—The *alligator pear* contains a relatively high fat content

SECOND WEEK

7 00 A.M.—Glass of milk and cream
2 heaping tablespoonfuls of well-cooked cereal
1 teaspoonful sugar
1 slice toast and butter
9 00 A.M.—Glass of milk and cream.
11 00 A.M.—Glass of milk and cream
2 zwiebacks Holland rusks Graham or Uneeda crackers
1 00 P.M.—Glass of milk and cream
1 egg, medium or hard boiled
1 portion applesauce
2 slices toast and butter
3 00 P.M.—Glass of milk and cream
2 zwiebacks Holland rusks Graham or Uneeda crackers
5 00 P.M.—Glass of milk and cream
7 00 P.M.—Cream soup (celery pea, spinach, etc.)
Baked potato with butter
Pulp of baked apple or skinned well-cooked prunes
1 slice bread and butter
9 00 P.M.
and
11 00 P.M.—Glass of milk and cream.
If patient is wakeful give milk and cream after 11 P.M.

THIRD WEEK

7 00 A.M.—Juice of ½ orange
Well-cooked cereal with milk cream and sugar
Toast and butter
Glass of milk and cream
9 00 A.M.—Toast and butter
Glass of milk and cream
11 00 A.M.—Glass of milk and cream
1 00 P.M.—1 egg
Mashed or baked potato
Applesauce or cornstarch rice or tapioca pudding
Toast and butter
Glass of milk and cream.
3 00 P.M.—Glass of milk and cream
5 00 P.M.—Glass of milk and cream
Toast and butter
7 00 P.M.—Cream soup (celery pea spinach etc)
1 soft-cooked egg
Stewed fruit puree or pulp of baked apple, or skinned well-cooked prunes
Glass of milk and cream
9 00 P.M.—Toast and butter
Glass of milk and cream
11 00 P.M.—Glass of milk and cream

FOURTH WEEK

Take milk and cream every two hours other foods at regular three meals One portion of any tender meat or fish may be substituted for eggs Gradually add puree of asparagus carrots peas spinach string beans and similar vegetables

THE MEULENGRACHT MODIFICATION—A more recent modification of the peptic ulcer regime has been suggested by Meulengracht This provides a much better balance and a more generous intake than that provided by the modified Sippy routine

FIRST DAY

6 00 A.M.—White bread and butter tea
9 00 A.M.—Oatmeal with milk, white bread and butter

TABLE 42.—COMPOSITION AND ENERGY VALUE OF SOUPS*

Variety	Percentage by weight			Total calories	
	Carbohydrates other than fiber	Protein	Fat	Per pound	Per 100 gram
Cream of asparagus[m]	3.8	0.8	3.3	217	48
Cream of celery[m]	4.4	0.9	5.1	304	67
Cream of mushroom[m]	5.5	1.7	2.5	233	52
Cream of oyster[m]	4.4	1.5	1.7	176	39
Cream of pea[m]	6.4	2.0	3.6	299	66
Cream of spinach[m]	5.6	1.9	5.9	376	83
Cream of tomato[m]	9.0	1.2	2.4	283	62
Tomato bouillon	0.4	1.1	0.3	39	9
Bean with smoked pork[m]	8.3	5.3	4.2	417	92
Gumbo creole[m]	3.0	0.7	0.3	103	23
Chicken noodle[ew]	4.3	1.6	1.0	148	32
Chicken soup (country)[w]	3.7	1.3	1.1	136	30
Clam chowder	4.2	1.8	1.0	150	33
Consomme	trace	3.7	trace	67	15
Consomme madrilene	0.6	2.8	trace	62	14
Corn chowder[m]	8.2	1.5	2.9	293	65
Mock turtle[ew]	5.4	1.6	0.5	147	32
Onion[m]	2.9	1.8	2.4	183	40
Pepper pot[m]	5.0	2.3	1.3	186	41
Scotch broth[m]	3.7	2.0	5.5	327	72
Turtle—genuine[m]	3.4	1.1	0.4	95	22
Vegetable beef	4.6	2.2	0.9	160	35
Vegetable (with beef stock)	5.0	1.4	1.1	160	36
Vegetarian vegetable	4.0	1.0	0.8	123	27

* From brochure on Nutrition published by H. J. Heinz Company
e = eggs
w = wheat
m = milk

large quantities The effectiveness of the rough diet is enhanced by the administration of lactose and other carbohydrate foods which tend to form gas Commonly the administration of the bulk diet is accompanied by the use of a lubricant such as petrolatum and/or a hygroscopic substance such as agar agar The latter takes up water and the swelling greatly increases the bulk of the stool

Type Diet

BREAKFAST

Glass of fruit juice
Fresh dried or stewed fruit
Whole grain or coarse cereal with cream and sugar
Egg
Whole wheat toast or bran muffin with butter and honey
Glass of buttermilk acidophilus or fermented milk

DINNER

Vegetable soup
Meat
Potato with skin
Vegetable
Salad with oil dressing or mayonnaise
Fresh dried or stewed fruit
Whole wheat toast or bran muffin with butter and honey
Glass of buttermilk acidophilus or fermented milk

SUPPER OR LUNCHEON

Egg or meat no cheese
Vegetable
Salad with oil dressing
Fresh dried or stewed fruit
Whole wheat bread or bran muffin with butter or honey
Glass of buttermilk, acidophilus or fermented milk

BETWEEN MEALS

Raw apple with skin or any raw fruit

THE LOW CALORY DIET

Indications —The low calory diet is widely employed in private practice for weight reduction It is also used in the management of patients with acute *coronary thrombosis* It is of the greatest importance that the low calory diet be balanced and in keeping with the maintenance of good health (p 697)

The adequate low calory diet calls for a mixed well balanced intake The caloric requirement is curtailed so that a gradual and progressive weight reduction is obtained over the course of weeks To be successful the diet should be one on which the patient may continue to subsist for long periods of time

Adjuvants for Weight Reduction —Adjuvants to assist in weight reduction may be employed with the low calory diet Low basal metabolic rates should be corrected by the administration of *thyroid extract* (p 1189) Unless there is a contra indication such as hypertension *amphetamine sulfate* (p 12) may be used to produce a loss of appetite

For the sweetening of beverages and in cooking saccharin is substituted for sugar Salt is used sparingly in cooking and should be avoided at the table

TABLE 45 —COMPOSITION OF MISCELLANEOUS FOODS*

Name	Percentage by weight			Calories per 100 grams	Total calories	Average portion	
	Protein	Carbohydrate other than fiber	Fat			Measure	Weight grams
Apple pie	1.6	32.0	9.1	216	287	1 piece—⅙ pie	133
Cake devils food iced	6.2	64.1	8.1	354	202	1 piece	57
Cake sponge	7.9	54.2	5.0	293	73	1 piece	25
Chocolate sweetened	2.0	58.6	29.8	511	291		57
Chocolate unsweetened	5.5	15.4	52.9	560	28	1 tablespoonful	5
Cocoa	9.0	26.2	18.8	310	19	2 tablespoonfuls	6
Corn syrup	0.0	74.0	0.0	296	62	1 tablespoonful	21
Crackers soda	9.6	72.5	9.6	415	104	4	25
Doughnuts	6.6	52.5	21.0	425	242	1	57
Honey	0.3	79.5	0.0	319	80	1 tablespoonful	25
Maple syrup	0.0	64.0	0.0	256	64	1 tablespoonful	25
Marmalade orange	0.6	84.5	0.1	341	85	1 tablespoonful	25
Molasses	2.1	69.3	0.0	286	100	1½ tablespoonfuls	35
Peanut butter	26.1	19.0	47.8	611	104	1 tablespoonful	17
Pretzels	8.8	74.2	3.2	361	90	6	25
Sugar							
Granulated (sucrose)	0.0	99.5	0.0	398	100	2 tablespoonfuls	25
Brown	0.4	95.5	0.0	384	69	2 tablespoonfuls	18
Date pudding[e w]	48.2	3.5	9.9	296			
Fig pudding[e w]	49.0	4.0	12.1	321			
Plum pudding[e w]	46.9	4.2	10.3	297			
Mince meat	45.1	2.8	2.0	218			

* From a brochure on Nutrition published by H J Heinz Company

e = eggs
w = wheat
m = milk

AFTER TWELFTH DAY

Continue above diet or gradually add soft foods as ordered.

HIGH CALORY DIET

Indications.—The high calory diet is employed (1) to maintain nutrition and conserve body weight during the course of prolonged *febrile disturbances* (2) in *hyperthyroidism* and (3) in the management of the patient who for one reason or another desires *to gain weight* (p 699)

The febrile patient who is confined to bed must be given the high calory feeding in a concentrated liquid form Under these circumstances the greatest tact and patience must be displayed by the nursing attendant Excessive zeal may lead to a complete breakdown of the appetite mechanism The high calory diet will not be accomplished without judicious coaxing and persistence

Adjuvants—Some patients do well with the conventional three meals Others accomplish more by frequent small feedings The flagging appetite may be stimulated by injections of insulin the judicious use of alcohol in the popular cocktail and by the serving of food that both looks and smells appetizing

Type Diet 4000 Calories

7 00 A.M.

Fruit juice 1 cup orange juice 1 tablespoonful lactose
1 egg soft boiled or in milk as egg nog
Bread 1 slice, plain or toasted 1 pat butter 1 tablespoonful jelly
Milk and cream ¾ cup milk ¼ cup of 20 per cent cream

9 00 A.M.

Cereal ½ cup cooked cereal (20 gm before cooking)
1 tablespoonful lactose ¼ cup 20 per cent cream
Cocoa ¾ cup milk, ¼ cup 20 per cent cream 1 tablespoonful cocoa

11 00 A.M.

1 egg in milk as eggnog or soft boiled
Bread 2 slices bread plain or toasted 2 pats of butter 2 tablespoonfuls jelly
Milk and cream ¾ cup milk, ¼ cup 20 per cent cream

1 00 P.M.

Mashed potato ½ cup mashed potato 1 pat butter
Chocolate malted milk bring to boil with small amount of water
2 tablespoonfuls lactose 1 teaspoonful cocoa
Add ¾ cup milk ¼ cup 20 per cent cream 2 teaspoonfuls malted milk powder

3 00 P.M.

Bread 1 slice bread 1 pat butter 1 tablespoonful honey
Vegetable ½ cup 9 per cent vegetable puree 1 pat butter
Custard ¾ cup milk 1 egg 1 tablespoonful sugar

5 00 P.M.

Cereal ½ cup cooked cereal 1 tablespoonful lactose
¼ cup 20 per cent cream
Milk and cream ¾ cup milk ¼ cup 20 per cent cream

7 00 P.M.

Eggnog ¾ cup milk, ¼ cup 20 per cent cream 1 egg 1 tablespoonful lactose
Applesauce sweetened ½ cup

Carbonated Drinks

The charged drink may be plain carbonated water artificially flavored carbonated drinks (cream soda lemon and orange soda) or cola drinks (containing caffeine carbonated water, and flavoring) Their nutritional value depends upon their sugar content In forcing fluids (p 664) they often provide a welcome change from fruit juice which may cloy the taste of the patient

Alcoholic Drinks

Although alcohol contains readily available nutritional elements (72 cc. produce 500 calories) it should not be employed as an important food source for obvious reasons In small quantities however it finds therapeutic use in promoting relaxation and improving appetite and digestion See *Alcohol Pharmacology of* (p 3847)

Coffee Tea and Cocoa

Coffee and Tea —Coffee and tea produce mildly stimulating effects dependent upon the caffeine content By slowing the gastric emptying time they also provide satiety value at the end of a meal Excessive use causes over stimulation nervousness insomnia nocturia from the diuretic action and in susceptible individuals rapid heart action

Decaffeinated beverages retain the flavor of coffee and lack the unpleasant cerebral effect in the susceptible

Cocoa —The chief value of cocoa besides its pleasant taste lies in the milk and sugar added to it Its alkaloid theobromine produces no stimulation Hot cocoa is often used as a mild bedtime sedative although it contains no pharmacological sedative principles

METHODS OF PREPARING AND PRESERVING FOODS (PHARMACY OF NUTRITION)

The Pharmacopeia of Nutrition lists the common foods which furnish the constituents of the normal dietary The preparation of foods, comparable to the pharmacy of drugs modifies the chemical and physical characteristics of the dietary ingredients

Cooking —The commonest type of food processing is *cooking* which increases the palatability and digestibility of many edibles The cooking of meats softens the connective tissue makes chewing easier and provides readier access for the digestive juices The starch granules in vegetables are burst by cooking thus assisting the effectiveness of the digestive enzymes

Despite its advantages cooking may result in the loss of considerable food value Vitamins may be destroyed by oxidation They may go into solution in the cooking water that is discarded This loss is avoided to some extent by pressure cooking

Canning —Canning processes have reached such a state of perfection that canned foods are often more nutritious and delicious than so-called fresh food Cooking after sealing makes for sterility and long time preservation as well as diminished loss of vitamins by oxidation Vitamins A B and D are well preserved in canned foods

Foods Chosen —At least 500 gm of carbohydrates should be ingested This is accomplished by giving high carbohydrates fruits and vegetables lactose cakes candies honey jams marshmallows syrup with wheat cakes and honey Spaghetti macaroni and noodles are also of service Meat *should be strictly limited and only* the lean portions allowed Butter egg yolks and cheese with high fat content should be avoided but cottage *cheese and egg* white are permissible

Adjuvants —Since the diet is low in fat it is advisable to give supplementary feedings of vitamins A D and K and of choline Because most of the calories are derived from carbohydrate large amounts of the B group of vitamins should be given

Type Diet —The following diet supplies 500 gm of carbohydrate and a total caloric intake of about 2300

BREAKFAST

1 cup 10 per cent fruit juice (p 649)
1 tablespoonful sugar
1 large banana, 1 tablespoonful sugar
6 tablespoonfuls cereal (dry) 1 tablespoonful sugar
2 slices bread 1 tablespoonful jam or honey
Coffee or tea sweetened with lactose

MIDDAY MEAL

1 large baked potato
¾ cup 10 per cent vegetable (645)
1 small salad of 5 per cent vegetable
1 portion pudding or cake with icing
1 large portion 18 per cent fruit (p 649) 1 tablespoonful sugar
2 slices bread
Coffee or tea, sweetened with lactose

SUPPER

¾ cup cooked rice
¾ cup 15 per cent vegetable (p 64)
¾ cup 10 per cent vegetable (p 645)
1 portion pudding or cake with icing
1 large portion 15 per cent fruit (p 64)
1 tablespoonful sugar
2 slices bread 1 tablespoonful jam or honey
Coffee or tea sweetened with lactose

Between meals it may be possible to persuade the patient to take lactose enriched fruit juices at frequent intervals This will also serve to increase the carbohydrate intake Hard candy is an excellent source of carbohydrate (p 2276)

HIGH CARBOHYDRATE—LOW PROTEIN DIET

Indications —This diet used in *azotemia* contains 500 gm carbohydrate 45 gm protein 45 gm fat

BREAKFAST

1 cup 18 per cent fruit (p 649)
3 tablespoonfuls cereal *(measured dry)*
¼ cup 40 per cent cream
1 tablespoonful sugar
1 slice bread 1 tablespoonful jam

10 00 A M

1 cup 10 per cent fruit juice (p 649) 1 tablespoon sugar or lactose

CHAPTER 31

METABOLISM PRACTICAL DIETOTHERAPY

PRACTICAL dietotherapy consists of the nutritional prescription given by the practitioner to his patient The directions call for the administration of the required and indicated foodstuffs to meet the individual metabolic need

THE NORMAL OR ADEQUATE DIET UNDER AVERAGE OR PHYSIOLOGICAL CONDITIONS

The Food and Nutrition Committee of the National Research Council has prepared a dietary yardstick (Table 47) tabulating the daily needs and requirements of the specific essential nutrients

FEEDING THE NORMAL INFANT

See p 2756

DIET IN CHILDHOOD

See p 2756

LOW PROTEIN—LOW SALT DIET

Indications.—In *nephritis with edema and nitrogen retention* the protein intake is reduced and fluids and salt are given in limited amounts in order to lessen water and nitrogen metabolism (p 2276)

Type Diet

BREAKFAST

1 cup orange juice 5 prunes, 1 tablespoonful sugar
1 tablespoonful oatmeal measured dry
1 tablespoonful sugar
¼ cup 40 per cent cream
1 egg
1 thin slice bread 1 tablespoonful sweet butter

MIDDAY MEAL

½ cup mashed potato
2 teaspoonfuls sweet butter
½ cup cauliflower 2 teaspoonfuls sweet butter
1 large leaf lettuce.
3 slices cucumber
2 teaspoonfuls mayonnaise without salt.
½ cup pineapple 1 tablespoonful sugar
1 thin slice bread, without salt, 2 teaspoonfuls sweet butter

SUPPER

1 medium baked potato
2 teaspoonfuls sweet butter
½ cup string beans 2 teaspoonfuls sweet butter
2 or 3 large lettuce leaves 3 slices tomato
2 teaspoonfuls mayonnaise salt free
1 tablespoonful sugar mixed with ½ egg and ¼ cup of 40 per cent cream
1 thin slice salt free bread
2 teaspoonfuls sweet butter

This diet contains about 0 7 gm of salt, assuming that no salt has been added at the table or in the preparation of the food.

In the absence of appreciable azotemia there is no need for protein limitation Low protein diets accelerate the downhill course in nephritis by failing to meet the requirements which are increased by albuminuria In the era of protein limitation many nephritics suffered more from malnutrition and dietary anemia than from renal insufficiency

KETOGENIC (HIGH FAT) DIET

Indications—The ketogenic diet has found great favor in the treatment of *epilepsy* and *urinary tract infections* With the development of efficient anticonvulsant drugs for the former and the use of sulfonamides mandelic acid and acid forming salts in the latter it has become less popular

Principles.—The diet includes minimal amounts of carbohydrates and maximum quantities of high fat foods such as cream butter oil oil dressings and fat meats such as pork duck goose Patients on this diet should receive careful and continual medical supervision

No foods except those prescribed in the diet may be given The patient is to avoid syrups elixirs sugar-coated tablets alkaline cathartics chewing tobacco chewing gum and candy

Type Diet

BREAKFAST

½ cup 5 per cent fruit (p 649)
2 strips bacon.
1 soy bean muffin 1¼ tablespoonfuls
¼ cup 40 per cent cream

THE ADEQUATE DIET FOR THE NORMAL ADULT

Given free choice man instinctively chooses a fairly adequate and balanced diet Deprived of metabolic necessities the body is capable of extraordinary adjustments as in starvation (p 584)

The diet of the normal adult is a variable Modern civilization imposes many modifications upon the demands of the normal appetite Thus the underprivileged may be compelled to subsist on a monotonous diet deficient in the more expensive footstuffs, such as meat the city dweller if he is addicted to counter meals is often constipated because of the low res due intake The alcoholic who obtains most of his calories from beverages may develop deficiency symptoms from the paucity of his remaining pabulum

The Metabolic Requirements—The dietary intake of the healthy adult must maintain normal weight promote normal growth and tissue replacement

Calorigenic Needs—The calorigenic requirement for basal needs approximates 10 calories for each pound of body weight Thus the average 150 pound individual requires 1500 calories daily for his basal needs To this basal caloric requirement must be added an additional 10 per cent for the activities of patients who are in bed approximately 20 per cent for those who are sedentary and as much as 50 to 100 per cent for those who are engaged in manual labor The total energy requirement may vary from 1500 calories for the basal need of the average adult to 4000 or 5000 calories necessary for the maintenance of body weight in those who do heavy labor

Protein Requirement—The total daily calories are supplied by the energy producing foods (protein carbohydrates and fat) Of the three the protein requirement is the most important

The biological quality of the protein food is important To obtain amino acids of highest biological value requires the incorporation in the protein intake of the best sources such as eggs milk kidneys liver, the muscle meats poultry fish soy beans potato cereal and most of the root vegetables

It is generally agreed that the protein intake should be at least 0.5 gm per pound of body weight or approximately 70 gm daily for the average adult weighing 150 pounds Since 1 gm of protein yields 4 calories the protein of the diet will furnish 300 of the total daily calories or approximately 15 per cent The remaining 85 per cent of the total calories are provided by the carbohydrate and the fat

Fat Carbohydrate Ratio—The proportion of carbohydrate calories to fat calories should be in the ratio of at least 2 to 1 and preferably 3 to 1 The carbohydrate should therefore yield approximately 60 per cent of the total calories and the fat the remaining 25 or 30 per cent Since 1 gm of carbohydrate yields but 4 calories as compared to the 9 calory yield from 1 gm of fat the dietary must contain 4 to 6 gm of carbohydrate for each gram of fat

Thus the breakdown of a 1500 calory intake for the basal daily requirement of a normal adult weighing 150 pounds would call for at least 75 gm of protein yielding 300 calories approximately 200 gm of carbohydrate yielding 800 calories and 40 gm of fat yielding 360 calories

TABLE 48 — PURINE CONTENT OF CERTAIN FOODS — *Continued*

List II *Foods which contain an insignificant amount* of purine or no purine

1 Beverages
  Carbonated
  Chocolate
  Coffee
  Fruit juices
  Postum
  Tea

2 Breads and breadstuffs (except whole grain in List III)
  Benson s water crackers
  Butter thins
  Corn bread
  Corn sticks
  French bread
  Gluten bread
  Holland rusk
  Soda crackers
  Uneeda biscuit
  Water rolls
  White bread
  Zwieback

3 Butter

4 Caviar

Cereals (e cept whole gra n in List III)
  Breakfast brownies
  Cornflakes
  Cream of wheat
  Farina
  Grits
  Post toasties
  Puffed rice
  Rice flakes
  Rice krispies
  White cornmeal
  Yellow cornmeal

6 Miscellaneous cereal products
  Arrowroot
  Hominy
  Macaroni
  Noodles
  Sago
  Spaghetti
  Tap oca
  Vermicelli

7 Cheese of all kinds

8 Eggs

9 Fats of all kinds (but eat in moderation)

10 Fruits of all kinds

11 Gelatin

12 Milk
  Buttermilk
  Condensed milk
  Malted milk

13 Nuts of all kinds
  Peanut butter

14 Pies (except mince meat)

15 Shad roe

16 Sugar and sweets

17 Vegetables
  Artichokes
  Beets
  Beet greens
  Broccoli
  Brussels sprouts
  Cabbage
  Carrots
  Celery
  Corn
  Cucumber
  Dandel on greens
  Eggplant
  Endive
  Kohlrabi
  Lettuce
  Okra
  Parsnips
  Potato
    Sw et
    White
  Pumpkin
  Rutabagas
  Sauerkraut
  String beans
  Summer squa h
  Swiss chard
  Tomato
  Turnips

18 Vegetable and cream soups (to be made with allowed vegetables and without meat stock)

19 Vitamin concentrates
  Cod liver oil
  Halibut liver oil
  Yeast

To calculate the pu ines or purine bodies in a given food the purine n trogen is multiplied by 3 *e g 200 mg of purine nitrogen equals 600 mg of purine bodies*

These foods are high in fat

are scrambled Cream is readily disguised in cocoa or cream soup and may form the basis for mousses and desserts as Bavarian cream It is of course usually acceptable whipped on fruit gelatin or with fruit Instead of regular gelatin d Zerta a gelatin substance with little or no food value may be used

LOW PURINE DIET

Indications — The low purine diet is employed in the treatment and prevention of gout (p 2867) The lists of foods in Table 48 show the rela

DINNER

Meat fish or poultry
Potato baked mashed creamed or boiled
One or two cooked *vegetables* (one green or yellow)
Bread and *butter* or *oleomargarine*
Salad
Dessert
Beverage such as tea or coffee

SUPPER OR LUNCHEON

A *creamed soup*
Egg or *cheese* or leftover *meat fish or poultry*
Bread and *butter* or *oleomargarine*
One *vegetable*
Salad
Dessert
A glass of *milk* or *cocoa*
Coffee or *tea*

Sufficient water should be imbibed with or between the meals so that the total fluids are brought up to a minimum of 2500 cc daily The daily urinary output should approximate 2000 cc or more

INDIVIDUAL VARIANTS IN THE DIET

Many individual factors modify the composition of the average normal diet Conventionally the average human eats three meals a day Occasionally individuals are found who eat only twice daily Those who work at night such as newspaper people and members of the musical and theatrical professions may arise late in the morning or at noontime and ingest but two meals in the course of the twenty four hours At the other extreme there are many whose stomachs empty rapidly and who demand frequent feedings to include a mid morning breakfast such as is given to school children the popular afternoon tea of the English or the bedtime snack so dear to the ice box raider

The city dweller commonly eats a sketchy and hurried breakfast as opposed to the generous morning meal of the farmer The opposite condition prevails with regard to the evening meal for the rural dweller will ingest a light supper whereas the principal meal in the city is taken in the evening

The diet of a fisherman is made up essentially of seafood The farmer partakes more generously of dairy products and the grains Families in the low income budget must eat sparingly of meat and animal fats

A successful dietary regime requires that it be fitted into the framework of the habits of the patient as well as those of the family group The overworked housewife cannot prepare a special diet for each ailing member of the clan as well as the usual meals for the remainder of the family

Psychic factors have much to do with the secretion of appetite juice and the digestibility of the meal The proverb states better is a dinner of herbs where love is than a stalled ox and hatred therewith

Individual experience is the keystone in the preparation of the normal diet Alvarez learned from his patients that distress was caused in individual instances by a variety of foods particularly onions the dairy products raw apples cooked cabbage chocolate radishes raw tomato cucumber a fat greasy and rich food cantaloupe meat and beef strawberries and coffee

MIDDAY MEAL

½ glass tomato juice
½ cup dried beans
⅔ cup cauliflower
3 apricots
2 slices Boston brown bread
1 glass milk or cocoa

3 00 P.M.

2 ounces milk chocolate

SUPPER

2 large clams
1 medium potato
⅔ cup Swiss chard
2 stalks celery
5 dried figs
2 slices whole wheat bread
1 glass milk
12 hazelnuts

8 00 P.M.

1 glass milk.
1 ounce cheese.
1 cracker

LOW CALCIUM DIET

Indications—In *hyperparathyroidism* with *hypercalcemia* and in certain types of *renal lithiasis* a low calcium diet is indicated to limit the degree of hypercalcinuria The elimination of milk cheese and eggs will usually diminish the calcium below the normal daily requirements

Foods poor in calcium include meat from fully grown animals fish potatoes fruit white bread refined flour coffee tea and sugar

The foods rich in calcium mentioned in connection with the high calcium diet are of course to be strictly avoided

Type Diet

BREAKFAST

½ medium grapefruit.
1 tablespoonful farina, measured dry
2½ ounces meat.
2 slices wheat bread
Sugar
Coffee or tea

MIDDAY MEAL

2½ ounces meat
¼ cup rice
½ cup squash
1 medium tomato
1 medium pear
1 slice white bread

SUPPER

2½ ounces meat
1 medium potato
¼ cup corn
1 serving lettuce
1 slice pineapple
1 slice white bread
Sugar
Oil dressing

The Diet in the Aged

The basal requirements of older patients are decidedly less than those of the adult Older people become progressively more sedentary so that the work calories are likewise appreciably reduced

An important complication of nutrition in older patients is *difficulty in mastication* Those who have lost teeth or have imperfectly fitting dentures and finally those who are completely edentulous require feedings of soft food that has been cooked and mashed Mineral and vitamin deficiencies are prone to occur unless supplementary preparations are added

SPECIAL DIETS

In the management of *disease conditions* special diets may be prepared (1) to protect the digestive organs (2) to spare the excretory channels, (3) to correct a nutritional deficiency or abnormality (4) to combat a metabolic derangement As with the normal diet these regimens must be modified according to the individual tastes habits preferences and economic status of the patient The printed lists avail little unless they are discussed with the patient and fitted into his mold

Forced Fluids

The forcing of fluids in the dietary requires the cooperation of the patient together with skill and persistence on the part of the nursing attendant Fluids may be taken with or between meals Most patients tolerate cold in preference to hot fluids Iced drinks can be taken in limited quantities Carbonated fluids while they appear tempting at first may cause distention and flatulence In nauseated patients they have a sedative effect The fruit drinks and flavored beverages soon cloy Usually in the end cool fresh water (Adam s cider) proves to be the liquid of choice

In the presence of *vomiting* or *lack of cooperation* on the part of the patient parenteral fluid may be given subcutaneously intravenously or by rectum

The Dehydration Diet

Indications —Dehydration is employed in the treatment of *epilepsy* and other *convulsive states* and also in *edema* and *anasarca* (p 706)

Chosen Foods —The total fluid should be limited to three or four glasses daily Salty and highly seasoned foods are avoided

The foods are chosen from the following list

Meat
Dairy products including eggs butter cheese custard
Fruit including banana fig prune grapes pears
Bread and *cereals*
Vegetables including potato beets carrots corn dried beans lima beans parsnips peas artichokes

Preparation of Foods —Vegetables are preferably steamed If they are prepared by boiling the water is drained An adequate vitamin intake requires at least one raw vegetable

Type Diet

BREAKFAST

Cereal with cream and sugar
Eggs
Bread and butter
Coffee or tea, with cream and sugar

MIDDAY MEAL

Meat soup if desired
Meat fish or chicken
Macaroni rice or any cereal
Corn or lentils
Rice pudding, egg pudding or cake
Coffee or tea
Cream and sugar

SUPPER

Meat soup if desired
Meat, egg American cheese or peanut butter
Macaroni or any cereal
Corn or lentils
Bread and butter
Coffee or tea, with cream and sugar

The diet being deficient in vitamin C should be supplemented with 50 or 60 mg of ascorbic acid daily

ALKALINE ASH DIET

Indications —*Uric acid urinary calculi* acute *nephritis* toxic degenerative *nephropathies* due to *metallic poisoning* and *bladder irritability* suggest the use of the alkaline ash diet

Principles —The alkaline ash diet is exactly the reverse of the acid ash diet since fruits vegetables and potatoes form the main portions of the regime Meat bread and cereals should be given only in small amounts All the common vegetables and practically all the common fruits may be used Extra amounts of fruit juice are indicated Bread products are confined to potato flour and lima bean flour muffins Butter cornstarch or tapioca may be used to fill out the caloric needs

Acid forming foods such as constitute the major part of the acid ash diet must be avoided

Type Diet

BREAKFAST

Fruit
Potato flour or lima bean muffin with butter and jam
Glass of milk
Glass of grapefruit juice or orange juice

DINNER OR SUPPER

Vegetable cream soup or tomato juice
Cheese
Potato any style
Vegetable
Salad
Fruit with sugar and cream if desired
Potato flour muffin or lima bean muffin butter or jam
Glass of milk or buttermilk
Glass of grapefruit or orange juice

2 Eggnog (one cup milk one egg one teaspoon sugar)
3 Fruit juice (one cup of fruit juice one egg white, one tablespoon sugar)
4 Vegetable soup (one half cup 18 per cent vegetable puree 1 cup milk one half pat butter)
5 Fresh vegetable juice (one cup mixed juice)
6 Chocolate milk (one cup milk 2 tablespoonfuls sugar 4 teaspoonfuls cocoa)
7 Custard (one cup milk 1 egg tablespoon sugar)
8 Cereal (one half cup of thick gruel one half cup milk one tablespoonful sugar
9 Vegetable juice (one cup tomato juice)
10 Chocolate egg nog (one cup milk one egg 2 tablespoonfuls sugar 4 teaspoonsfuls cocoa)
11 Vegetable soup (one half cup 9 per cent vegetable puree 1 cup milk 1 pat butter)
12 Fruit juice (one cup 9 per cent fruit juice 1 egg white 1 tablespoon sugar)

The Bland Gastric Diet

Indications—The bland diet has found widespread employment in the treatment of *gastritis duodenitis* and *gastro duodenal ulcer* The most popular is the dietary suggested by Sippy (p 1780)

Sippy Regime—The original Sippy diet calls for the preparation of a mixture of equal parts of milk and cream On the first second and third days of treatment the patient is given 3 ounces of this mixture every hour from 7 A M to 7 P M The mixture is preferably served cold or slightly chilled

From the third to the tenth days the milk and cream mixture is continued In addition the patient receives a soft boiled egg and a well-cooked cereal The amounts are increased until by the tenth day the total daily dietary includes 3 ounces of the mixture hourly from 7 A M to 7 P M a soft boiled egg served at 7 A M noon and 7 P M and 3 ounces of cereal served with the mixture at 10 A M 1 P M and 4 P M

MODIFIED SIPPY REGIME—For various reasons the original Sippy regimen has been modified The objections to the continuation of the routine include the monotony of the diet the vitamin and particularly iron deficiency the unnecessary rigidity of the regimen and the absence of food intake from 7 P M to 7 A M

First Two Days

7 00 A.M–11 00 P M

½ glass milk and cream (¼ cream, ¾ milk) every two hours If patient is wakeful give mixture after 11 00 P.M

Third and Fourth Days

Same as above Add two heaping tablespoonfuls of well cooked cereal twice a day morning and evening A teaspoon of sugar and the usual glass of milk and cream may be used with the cereal

Fifth Sixth and Seventh Days

Same as above Add 1 egg and 1 slice of bread or toast and butter at noon

BETWEEN MEALS

Eggnog beef juice
Sandwiches of whole wheat bread
Milk drinks
Use honey or molasses instead of sugar throughout.

ELIMINATION DIETS

Indications—In the presence of suspected *food allergy* where the history is not clearcut various foods may be eliminated one at a time by a series of elimination diets devised by Rowe (p 547)

It is clear that certain of these diets are deficient in vitamins For example Diet IV contains only milk and the other diets exclude milk For safety s sake it is wise to administer vitamin concentrates as supplements to the diet and where milk has been omitted to give tablets of calcium gluconate

Technic—The patient is placed on one or the other of these dietary regimes for a period ranging from ten days to three or four weeks During that time he must adhere strictly to the diet and take no other food whatsoever It is advisable for him not to eat in a restaurant where the ingredients of his food can never be completely known to him

Type Diets

DIET I

(No milk rye beef pork poultry corn)

Rice tapioca, rice biscuit, rice bread
Lettuce spinach carrots beets artichokes
Lamb
Lemon, grapefruit, pears.
Cane sugar
Wesson oil, olive oil, salt.
Gelatin, syrup made of maple sugar or cane sugar flavored with Mapleine or maple sugar
Olives
Peanut butter

DIET II

(No lamb beef rice milk)

Corn, rye corn pone corn rye muffins rye bread rye crisp
Tomato squash asparagus peas string beans
Chicken bacon
Pineapple peaches apricots prunes
Cane sugar
Mazola oil Wesson oil salt.
Karo corn syrup
Gelatin

DIET III

(No rice lamb poultry milk rye)

Tapioca
White and sweet potato lima bean potato bread soy bean lima bean bread
Beets carrots lima beans string beans tomato
Bacon beef
Lemon grapefruit, peaches apricots
Cane sugar
Olive oil Wesson oil gelatin salt
Olives
Maple syrup or syrup made with cane sugar flavored with maple

DIET IV

Milk, up to two or three quarts a day
Tapioca cooked with milk and milk sugar may also be taken

2 Eggnog (one cup milk one egg one teaspoon sugar)
3 Fruit juice (one cup of fruit juice one egg white, one tablespoon sugar)
4 Vegetable soup (one half cup 18 per cent vegetable puree 1 cup milk one half pat butter)
5 Fresh vegetable juice (one cup mixed juice)
6 Chocolate milk (one cup milk 2 tablespoonfuls sugar, 4 teaspoonfuls cocoa)
7 Custard (one cup milk 1 egg, tablespoon sugar)
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PREOPERATIVE DIET FOR PATIENTS WITH LESIONS OF STOMACH OR DUODENUM

	First week	Second week	Third week	Fourth week	Ambulatory
Mixture of equal parts milk and cream * cc per hour	1 0	1 0	90	90	†
Breakfast					
Bland cereal cup		½	½	½	½
Cream cup		¼	¼	¼	½
Toast, melba, piece			1	2	2
Butter square			½	1	1
Bland fruit serving					1
Egg				1	1
Postum cup					1
Orange juice cc				30	60
Noon Meal					
Cream soup strained cup			¾	¾	¾
Potato serving				1	1
Meat serving (50 gm)					1
Vegetabl puree serving					1
Dessert, bland serving			1	1	1
Toast melba piece			1	2	2
Butter square			½	1	1
Cream tablespoonful					2
Postum cup					1
Orange juice cc				30	60
Evening Meal					
Bland cereal or cream soup cup			½		
Milk toast egg or custard serving			1	1	1
Potato or substitute serving					1
Vegetable puree serving					1
Dessert bland serving				1	
Toast melba piece			1	2	2
Butter square			½	1	1
Cream tablespoonful					2
Fruit serving					1
Postum cup					1
Orange juice cc				30	60
Composition (approximate)					
Carbohydrate gm	90	105	132	156	221
Protein gm	4	5	60	71	82
Fat gm	216	203	180	215	1 9
Calories	2 20	2 467	2 469	2 903	2 643

Foods Permitted —Bread melba toast, zwieback rusk Fruit cooked pears peaches apricots white cherries applesauce baked apple banana (very ripe or baked) avocado Potato baked creamed escalloped mashed Potato substitutes macaroni rice spaghetti noodles Desserts bland (without fruits nuts or cocoanut) angel food cake sponge cake jello and gelatin desserts ice cream tapioca pudding rice pudding cornstarch pudding Cereal cream of wheat cornmeal farina, strained oatmeal (In the diet for ambulatory patients only cornflakes puffed rice rice flakes rice krispies) Meat calf liver chicken fish oysters scraped beef sweetbreads Cheese cottage and cream Beverage Postum weak cocoa Salt sugar concentrated sweets in small amounts

Foods Excluded —Meat and fish other than those listed whole grain breads cereal products fresh breads muffins hot biscuits or rolls raw vegetables whole cooked vegetables fruits other than those listed desserts other than those listed meat soups gravies pepper spices condiments cheeses other than those listed fried foods nuts coffee and tea

* A feeding of milk and cream is offered every hour from 7:30 A M to 9 30 P M on the diet for the first week on the diets for the second third and fourth weeks small meals replace three of the feedings

† Hourly feedings are discontinued on the diet for ambulatory patients a glass of mixture of two-thirds milk and one third cream is served at 10 A M 3 P M and 8 P M

1 00 P M —Pureed vegetable (peas carrots)
Mashed potato
Tea white bread and butter
3 00 P M —Cocoa or tea
6 00 P M —Cream cheese or eggs (soft boiled or poached)
Boiled or mashed potato or cereal with milk and sugar
Pureed vegetable
Dessert (from above list)
White bread and butter

The Bland Low Residue Diet

Indications —The bland low residue is employed wherever and whenever there is irritability or inflammation of the gastro intestinal tract This type of diet is especially useful in the management of *gastritis duodenitis gastroduodenal ulceration colitis* and the *diarrheal states* of all types in the *enteric fevers* as a *preoperative regime* particularly in the surgery of the large bowel *postoperatively* wherever there has been manipulation of the gastro intestinal tract

Foods Excluded —Raw fruits and vegetables bran whole wheat grain bread and cereal veal and pork are necessarily excluded Hence it is usually wise to supplement this diet with additional vitamins

Foods Chosen —The foods that leave the least residue include gelatin the sugars hard boiled eggs lean meat liver rice farina and cottage cheese

Preparation of Food —Vegetables are to be pureed or mashed The canned strained foods are particularly useful and palatable The skin of fruits and of root or tuberous vegetables and the leaves of stem vegetables should be removed Cereal must be well cooked in a double boiler The rough health foods are avoided

Type Diet —A typical low residue diet is undernoted

Breakfast

Strained orange grapefruit juice or stewed fruit
Eggs (soft or hard boiled or poached) or well-cooked cereal with milk and sugar
White bread or toast with butter or jelly
Buttermilk thin cocoa or tea

Noon Meal

Tomato juice
Small portion scraped beef lamb fish or minced white meat of chicken (not fried)
Boiled mashed or baked potato
Vegetables pureed or mashed
Stewed fruit or other simple desserts
White bread or toast with butter or jelly
Buttermilk thin cocoa or tea.

Supper

Milk soup with strained vegetables or clear soup
Egg soft or hard boiled or poached
Small portion cream or cottage cheese or well cooked cereal or strained vegetable
Fruit as above
White bread or toast, with butter or jelly
Buttermilk thin cocoa or tea

The High Roughage Diet

Indications —The high roughage diet is employed in the management of *atonic constipation* The rough and bulky foods are administered in

When there is *postoperative gastric retention* the fluid intake is restricted and dry bland foods such as cereals or rice are substituted

FORMULA FOR JEJUNAL FEEDING

	Day after operation					
	1*	2	3	4	5	6
Amount per hour cc	ɔ0	30	60	60	90	90
Total amount per day cc	720	720	1 440	1 440	2 160	2 160
INGREDIENTS Ice cream mixture gm †	1ɔ0	200	400	4 0	~00	800
Skimmed milk powder gm		25	50	60	75	75
Eggs whole			1	2	2	2
Egg yolks					1	2
Glucose gm	2ɔ	25	60	60	80	100
Ascorbic acid mg			25	50	ɔ0	50
Halibut liver oil, drops				15	15	15
Vitamin B Complex Elixir (Abbott) cc			60	60	60	60
Sodium chloride gm			5	5	5	5
Water cc.	5 0	5 0	900	890	1 310	1 210
COMPOSITION Carbohydrate gm	47	6ɔ	139	150	213	248
Protein gm	6	15	36	4C	64	71
Fat, gm	21	30	66	~9	1 1	141
Calories total	401	590	1 294	1 49	2 197	2 545
Calories per ounce (30 cc)	17	25	27	31	31	3ɔ

METHOD OF PREPARATION
Combine the skimmed milk powder with water to make a smooth paste Add remainder of water glucose and ice cream mixture Beat egg to them add halibut liver oil and beat again. Combine ingredients strain and add asc rbic ac d and V tamin B Complex Elixir The ascorbic acid should be dissolved in a small amount of water Individual feed ngs should be warmed over hot water to body temperature before administering

* Figure design tes the first day th t the formula is injected the consecutive figures refer to days aft r th formula was start d

† Ice cream mixture has the following composition per 100 gm carbohydrate 15 gm prote n 4 gm fat 14 gm

Fluids —Fluids may be restricted, but dehydration is to be condemned in the production of weight loss Dehydration by the use of saline cathartics or diuretics does not result in permanent weight loss nor does the ingestion of fluid with the meal increase the availability of the food of the dietary

Bulky foods produce a feeling of satiety in the otherwise normal individual and have a high satiety value However they may result in circulatory embarrassment in the cardiac invalid

Type Diet 1000 Calories —A simple low calory diet is the following

BREAKFAST

Fruit—raw or stewed without sugar
⅓ cup cereal with ½ cup milk
1 slice bread
Coffee without cream or sugar
1 glass skimmed milk.

DINNER

Broth if desired
4 ounces of meat fish or chicken
1 portion 5 per cent vegetable (p 645)
1 portion 10 per cent vegetable (p 645)
1 portion fruit—raw or stewed without sugar
1 slice bread
Clear tea or black coffee

SUPPER

2 eggs or 2 ounces cottage cheese
1 portion 5 per cent vegetable (p 645)
1 portion 10 per cent vegetable (p 645)
1 slice bread
Clear tea or black coffee
1 glass of skimmed milk or buttermilk

LOW CALORY—RESTRICTED FLUID DIET FOR THE CARDIAC INVALID (KARELL)

Prior to the introduction of the powerful diuretics the edematous *cardiac invalid* was commonly placed on a low calory restricted fluid diet of the type popularized by Karell (p 941)

Karell Type Diet

FIRST WEEK

8 00 A M —250 cc milk (1 glass)
12 00 noon—250 cc milk (1 glass)
4 00 P.M —250 cc milk (1 glass)
The milk may be cold or warm Give no other food or liquid

EIGHTH DAY

Same as above Add
10 00 A M —1 soft-cooked egg
6 00 P.M —2 slices dry toast or zwieback

NINTH DAY

10 00 A.M —Add 2 slices dry toast or zwieback.
6 00 P.M — 1 soft-cooked egg

TENTH ELEVENTH AND TWELFTH DAYS

12 00 noon—Add 1 soft-cooked egg
¼ cup boiled rice or rice cooked in milk
¼ cup vegetable puree (asparagus, carrot, pea)
2 slices dry toast or zwieback.
Scraped beef or tender chicken—if allowed

Additional Feedings

Fruit juice (10 a m 3 p m 8 p m)	1 glass
Candy plain sugar	ounces taken during day

DIETARY REGIMENS FOLLOWING VARIOUS OPERATIONS ON THE COLON

The following dietary regimens usually are used subsequent to the more common or representative surgical procedures indicated However there are no routine measures and each patient is considered individually

COLOSTOMY

Residue-free liquids until exteriorized loop of bowel is opened
Low residue diet† after loop of bowel is opened
Low residue diet increased as tolerated

ILEOCOLOSTOMY

Residue-free liquids beginning fourth postoperative day
Full residue-free diet ‡ sixth or seventh postoperative day
Low residue diet eighth or ninth postoperative day
Modified low residue diet, twelfth postoperative day

POSTERIOR RESECTION

Residue-free liquids beginning second postoperative day
Low residue diet as tolerated third postoperative day
Low residue diet increased as tolerated

EXTRAPERITONEAL RESECTION

Residue free liquids until exteriorized loop of bowel is opened
Low residue diet after loop of bowel is opened
Low residue diet increased as tolerated

COMBINED ABDOMINOPERINEAL RESECTION

Residue free liquids beginning second postoperative day
Low residue diet as tolerated third postoperative day
Low residue diet increased as tolerated

PAUL OR MIKULICZ PROCEDURE

Residue free liquids until exteriorized loop of bowel is opened
Low residue diet after loop of bowel is opened
Low residue diet increased as tolerated

ANTERIOR RESECTION WITH COLOSTOMY

Residue-free liquids until exteriorized loop of bowel is opened
Low residue diet after loop of bowel is opened
Low residue diet increased as tolerated

CLOSURE OF COLONIC STOMA

Residue-free liquids beginning fourth postoperative day
Full residue-free diet, sixth or seventh postoperative day
Low residue diet eighth or ninth postoperative day
Modified low residue diet, twelfth postoperative day

Residue free liquids are limited to strained fruit juices gelatin made with fruit juices and clear tea, coffee and broth

† The low residue diet is given on page 668

‡ The residue-free diet employed after operation is similar to the one used preoperatively except that it may include an egg and broth

9 00 P M

Chocolate malted milk Bring to boil with small amount of water
2 tablespoonfuls lactose 1 teaspoonful cocoa
Add ¾ cup milk and ¼ cup 20 per cent cream 2 teaspoonfuls malted milk powder
Bread and jelly 1 slice bread plain or toasted 1 pat butter 1 tablespoonful jelly

In the ambulatory patient an increased caloric intake may be provided by supplementary feedings of ice cream sodas ice cream sundaes with syrup nuts and whipped cream ice cream cones or similar frosted desserts

There is little doubt that the discontinuance of smoking permits a greater ingestion of food Individuals who suffer from the symptoms that accompany visceroptosis may gain weight when cigarettes are banned

A suggested high calory feeding for the ambulatory patient is under noted

Type Diet for Ambulatory Patient

BREAKFAST

Fruit with cream and sugar
Milk-cooked cereal with butter cream and sugar
Eggs with bacon (not crisp) ham or sausage
Rolls toast etc with butter and jam jelly honey or marmalade
Glass of milk and cream (3 1) egg nog or chocolate milk etc

10 00 A M

Glass of milk and cream (3 1) eggnog or chocolate milk

DINNER

Milk soup pea lentil or potato
Meat fish or chicken (or egg or cheese dish)
Potato with butter cream or cream sauce
Salad with dressing or cream
Dessert, as stewed fruit and cake with icing etc
Bread and butter with jam jelly honey peanut butter or marmalade
Glass of milk and cream (3 1)

3 00 P M

Glass of milk and cream (3 1) crackers and cheese fruit juice with lactose baked apple, cake or cookies

SUPPER OR LUNCHEON

Egg or cheese dish (or meat fish or chicken)
Potato with butter or cream sauce or sweet potato macaroni noodles spaghetti or waffles with syrup
Vegetable with butter cream or cream sauce
Salad with dressing or cream
Bread and butter with jam jelly honey marmalade or peanut butter
Milk pudding ice cream stewed fruit with sugar and cream or cake
Glass of milk and cream (3 1)

8 00 P M

Glass of milk with cream (3 1) hot malted milk
Crackers with cream cheese and jelly jam or honey

HIGH CARBOHYDRATE—LOW FAT DIET

Indications —For years the standard dietary treatment of *liver disease* has consisted in giving large amounts of carbohydrate with the exclusion of fat Recently it has been shown that the extractives associated with meat proteins are hepatotoxic in the presence of liver damage The protein requirements are best met by dairy products

CHAPTER 32

THE DIFFERENTIAL DIAGNOSIS AND MANAGEMENT OF THE COMMONER DISORDERS OF METABOLISM

Increased Growth (Gigantism)
Decreased Growth (Dwarfism Infantilism)
Diminution in Adult Size
Increased Weight (Obesity)
Decreased Weight (Loss of Weight, Cachexia)
Dehydration (Anhydremia, Desiccation)
Hyperhydration ("Bulk Reaction" Water Intoxication Hyperhydremia)
Decrease of Plasma Volume (Forward Failure)
Increase of Tissue Fluid (Edema, Anasarca)
Increased Basal Metabolic Rate
Decreased Basal Metabolic Rate
Fevers of Metabolic Origin
Disturbances of Hydrogen Ion Concentration
Acidosis
Alkalosis
Hypercalcemia
Hypocalcemia (Tetany)
Hyperphosphatemia
Hypophosphatemia
Disturbances of Serum Phosphatase
Hyponatremia
Hypernatremia
Hyperpotassemia
Hypopotassemia
Hyperchloremia
Hypochloremia
Hyperglycemia
Hypoglycemia
Reversal of Albumin Globulin Ratio
Hypoproteinemia
Azotemia
Hyperuricemia
Hypercholesteremia
Hypocholesteremia
Hyperlipemia

DISTURBANCES OF GROWTH

The growth of the human skeleton is dependent upon the interaction of a variety of exogenous and endogenous factors Amongst the former the presence in the diet of the amino acids tryptophane and lysine is essential for building new tissue In addition adequate supplies of calcium and the vitamins A and D are required since deficiencies of any of these building blocks may result in imperfect bone formation with subsequent deformity and shortening particularly under the stress of weight bearing The most important endogenous metabolic influence is exerted by the growth factor elaborated by acidophile cells of the anterior lobe of the pituitary gland Removal of this structure (hypophysectomy) results in infantilism whereas injections of a potent anterior pituitary liquid may produce experimental gigantism

In health the secretion of growth hormone is integrated with the activity of other endocrine systems notably thyroid gonads pancreas and adrenal cortex In most glandular interrelationships the pituitary factor is dominant In cretinism however absence of thyroid secretion seems capable of retarding growth without significant pituitary involvement and in pregnancy acromegaloid changes are observed secondary to the gravidity

Treatment of Increased Growth —The parents of the child whose rate of growth is physiologically increased require reassurance that the zone of pathologic endocrinopathy is rarely traversed The youngster should return at frequent intervals for observations of the rate of growth and if

MIDDAY MEAL

1 large potato
½ cup 15 per cent vegetable (p 645)
½ cup 10 per cent vegetable (p 645)
¾ cup 15 per cent fruit (p 649)
2 tablespoonfuls sugar or lactose
1 slice bread 1 tablespoonful jam or honey

3 00 P.M

1 cup 10 per cent fruit juice (p 649)
1 tablespoonful sugar or lactose

SUPPER

¾ cup cooked rice
½ cup 10 per cent vegetables (p 645)
1½ cup 5 per cent vegetables (p 645)
¾ cup 15 per cent fruit (p 649)
1 tablespoonful sugar or lactose
1 slice bread 1 tablespoonful jam or honey

8 00 P M

1 cup 15 per cent fruit juice (p 649)
1 tablespoonful sugar or lactose

HIGH PROTEIN—LOW FAT DIET

Indications —In *nephrosis* (p 2389) *with edema* the diet is enriched to make up for protein lost in the urine Because of the *lipemia* (p 758) present in this disease fats are restricted

Principles —The proteins should make up 20 to 25 per cent of the caloric requirements Salts and fluids are kept at a minimum, and carbohydrates are given in moderate amounts A sample diet of 1515 calories is given below it contains 150 gm carbohydrate 150 gm protein 35 gm fat

Type Diet

BREAKFAST

½ cup 10 per cent fruit (p 649)
2 eggs or 2 ounces of fish
1 slice bread 1 teaspoonful jam
1 cup skimmed milk
1 tablespoonful sugar

MIDDAY MEAL

6 ounces lean meat
½ cup 5 per cent vegetable (p 645)
1 medium 5 per cent vegetable salad (p 645)
1 ounce pot cheese (cottage cheese)
½ cup 15 per cent fruit (p 649)
1 slice bread
1 cup skimmed milk

SUPPER

6 ounces fish
½ cup 5 per cent vegetable (p 645)
1 medium 5 per cent vegetable salad (p 645)
1 ounce pot cheese (cottage cheese)
½ cup 15 per cent fruit (p 649)
1 slice bread, 1 teaspoonful jam.
1 cup skimmed milk.

Butter and other fat containing foods such as pie pastry foods prepared by frying, olive oil in dressings mayonnaise and the like may be added in cases of nutritional edema when lipids need not be restricted

DIFFERENTIAL DIAGNOSIS OF

Decreased Growth

The undersized child is frequently brought to the practitioner by an anxious parent. In most instances physical examination is normal and the cause of the stunting is a mere physiologic lag since growth often is delayed until the time of puberty

In the rare instance in which the practitioner is confronted with the problem of infantilism or dwarfism, an extensive survey is required in order to clarify the fundamental difficulty and to obtain specific indications for therapy The term infantilism is here applied to a proportionate diminution in stature whereas dwarfism connotes in addition, asymmetry and deformity

CAUSE	DIAGNOSTIC FEATURES
Physiologic Variants	Particularly familial and racial
Primary Hypopituitarism	Retardation of growth without distortion or deformity (Lorain Levi types) Premature senility in the variety described by Simmonds and Hutchinson Gilford Note therapeutic responses to anterior pituitary growth hormones with estrogen and/or androgen (p 2404)
Secondary Hypopituitarism	Infantilism resulting from profound physical or metabolic disturbances such as congenital heart disease neonatal syphilis diabetes mellitus celiac disease (pancreatic infantilism) severe rickets malnutrition hookworm infestation microcephalus hydrocephalus idiocy or prematurity (p 2763)
Achondroplasia	Dwarfism with disproportion and retardation of growth of extremities Head enlarged forehead prominent bridge of nose depressed abdomen protuberant, buttock prominent and lumbar lordosis increased.
Dyspituitarism	Obese dwarfism (p 1166) Shortening of arms and legs, round face atrophy of genitals and slight depression of BMR (Frohlich's syndrome) Note therapeutic responses to anterior pituitary growth hormones with estrogen and/or androgen (p 2404)
Hypothyroidism	Cretinous dwarfism (p 693) Idiotic facies mental and sexual retardation protuberance of abdomen, umbilical herniation, non pitting edema of skin, and marked depression of basal metabolic rate (p 719) Therapeutic response to thyroid extract (p 1189)
Mongolism	Idiocy with small skull flat occiput, thick lips open mouth, hypermotility of joints and characteristically obliquely set eyes.
Rickets	Dwarfism due to dietary deficiency Deformities at epiphyseal junctions Large square skull with frontal bosses Abnormalities of thoracic cage legs and teeth May have low levels for blood phosphorus Therapeutic response to administration of vitamin D (p 621)
Renal Rickets	Dwarfism associated with congenital aplasia of kidney or advanced renal damage (p 2240) May be associated with high levels for blood phosphorus Failure of response to vitamin D

MIDDAY MEAL

Clear broth
2 ounces meat
½ cup 5 per cent vegetable (p 645)
2 teaspoonfuls butter
¼ cup 5 per cent fruit (p 649)
¼ cup 40 per cent cream
1 soy bean muffin
1 tablespoonful butter

SUPPER

Broth
1 egg
½ cup 5 per cent vegetable (p 645)
2 tablespoonfuls mayonnaise
¼ cup 5 per cent fruit (p 649)
¼ cup 40 per cent cream
1 soy bean muffin
1¼ tablespoonfuls butter

Recipe for Soy Bean Muffins—Soy bean muffins are used because they contain small amounts of carbohydrate in comparison to that in bread flour One cup baker s bran 1 teaspoonful baking powder two thirds cup soy bean meal and one quarter teaspoonful salt are mixed Four tablespoonfuls butter are melted and added with two thirds cup water and 4 egg yolks to mixture The batter should be beaten until smooth and free from lumps Egg whites are beaten until stiff and folded into mixture The mixture is then placed in a muffin pan and baked in a hot oven This amount makes twelve muffins

Aids to Palatability—The ketogenic diet is rather unpalatable Various attempts have been made to disguise the large amounts of fat which go into it For example butter may be added to clear broth vegetables and dessert without intruding too much on the taste Peanut butter and cream cheese mixed with butter are all good sources of fat which are not too unpalatable Egg yolks may be used for garnishing or cooking Oil is unobtrusive in mayonnaise Bacon fat or butter blend well with eggs that

TABLE 48—PURINE CONTENT OF CERTAIN FOODS*

List I Foods which contain very large amounts (150–1000 mg) of purine bodies in 100 gm

Sweetbreads	8?? mg	Kidneys (beef)	200 mg
Anchovies	363 mg	Brains	19 mg
Sardines (in oil)	295 mg	Meat extracts	160 400 mg
Liver (calf beef)	233 mg	Gravies	

List II Foods which contain a large amount (75–150 mg) of purine bodies in 100 gm

Bacon beef calf tongue carp chicken soup codfish duck goose halibut lentils liver sausage meat soups partridge perch pheasant pigeon pike plaice pork quail rabbit sheep shellfish squab trout turkey veal venison

List III Foods which contain a moderate amount (up to 75 mg) of purine bodies in 100 gm

1 Asparagus bluefish bouillon cauliflower chicken crab eel finnan haddie ham herring kidney beans lima beans lobster mushrooms, mutton navy beans oatmeal oysters peas salmon shad spinach tripe tuna fish whitefish
2 Also whole grain bread and breadstuffs graham bread graham crackers oatmeal crackers rye bread Rye Krisp whole wheat bread Zed
3 Also whole grain cereals Bemax bran bran flakes cracked wheat, Fmbo graham porridge Grapenuts 'Krumbles malt breakfast food Pep bran flakes Pettijohn Puffed wheat, Ralston s Sims Shredded Wheat, Wheat[illegible] worth Whole Wheat Krumbles

DIFFERENTIAL DIAGNOSIS OF

Gain in Weight

Gain in weight may be due to the deposition of fat or the accumulation of fluid as is frequently encountered in congestive failure or the nephropathies Endocrine obesity is relatively rarely observed, popular opinion to the contrary notwithstanding

The deposition of fat is a distinctly individual phenomenon. Women tend to gather fat in the region of the buttocks whereas the male is more apt to present a heavy panniculus. Certain individuals, often on a familial basis, have heavy breasts or legs. This peculiarity is transmitted, with great faithfulness, from one generation to another

In the adult, gain in weight has not the invariably favorable connotation that prevails in the course of normal growth in infancy and childhood. Obesity predisposes to hyper tension and arteriosclerosis. Retention of body fluids suggests impending difficulty as the result of backward failure or renal insufficiency

CAUSE	DIAGNOSTIC FEATURES
Physiologic	May be racial or familial. Normal growth in children.
Hyperalimentary	With gluttony and increased caloric intake
Pregnancy	When gain exceeds 12 to 15 pounds.
Diminished Energy Output	In the sedentary and in patients confined to bed.
Retention of Salt and Water	Cardiac or nephritic edema. Look for accumulation of ascites (p 1921)
Psychogenic	Overeating associated with anxiety frustration, neuroses and psychoses.
Pharmacologic	Especially in chronic alcoholism due to beer drinking
Gastrogenous	From frequent feeding in gastric hypermotility and peptic ulcer
Hyperinsulinism	Functional manifestation in association with gluttony Less frequently from hypersecretion associated with adenoma of pancreas. Note hypoglycemia during periods of hunger
Dyspituitarism	Frohlich s syndrome (p. 1166) with rotund obesity fat accumulation about abdomen and side oligomenorrhea or amenorrhea, hypogonadism, sterility gynecomastia, slender ankles and wrists and diminished or absent libido and potency Get x ray of sella turcica
Pituitary Basophilism	Cushing syndrome (p 1159) with 'buffalo head, girdle obesity hypertension, glycosuria, linear striae of abdomen, and female hirsutism. Get x ray of sella turcica and region of adrenal cortex. Perform lumbar puncture and consult neurosurgeon.
Hypothyroidism	Cretinism and myxedema (p. 1191) with thickening of the skin, loss of eyebrows bradycardia hypothermia and diminution in the BMR. Therapeutic response to thyroid extract
Hypogonadism	In conjunction with the menopause male climacteric or castration. Obesity develops with regression of secondary sex characteristics.
Adiposis Dolorosa	Dercum s disease (p. 1174) with painful lipomatous masses.

tive purine content of the common edibles Those foods in Lists I and II should be avoided in the diet, the substances in List III should be chosen sparingly and those in List IV may be eaten freely The total caloric intake is best reduced to 10 to 15 per cent less than the calculated requirement It may be necessary to supplement the diet with artificial vitamin B complex

Type Diet

BREAKFAST

Fresh fruit
Cereal (List IV # 5)
Bread (List IV # 3) and butter)
Eggs
Milk

LUNCHEON AND DINNER

Soup (List IV # 18)
Meat, Fish and Poultry (List III Par 1 List IV # 4 15)
Vegetables (List IV # 17)
Dessert (List IV # 7 10 11 13 14 16)
Beverage (List IV # 1 12)

HIGH CALCIUM DIET

Indications—The calcium intake should be increased in *rickets tetany* due to hypoparathyroidism *hypocalcemia* associated with gastro intestinal disturbances such as sprue and in *pregnancy*

Principles—The best dietary source of calcium is milk one quart of which contains 1 2 gm Approximately 65 per cent of the calcium in a high calcium diet may easily be administered in the form of milk and milk products such as cheese Absorption may be facilitated and improved by the administration of vitamin D preparations

Other foods containing relatively large amounts of calcium are egg yolk clams lobster oysters shrimp meat from young animals dried kidney beans beet greens broccoli cauliflower turnip tops black bread whole grain cereals molasses nuts eggs oranges and maple syrup

It is advisable to avoid foods poor in calcium In the presence of hypo*parathyroidism the administration of calcium should be supplemented* by calcium salts parathyroid extract or dihydrotachysterol

Type Diet—A sample diet containing a little over 3 gm of calcium per day is given below

BREAKFAST

1 medium orange
2 tablespoonfuls oatmeal, measured dry
½ cup milk
2 eggs
2 slices whole wheat bread
1 glass milk or cocoa.

10 00 A.M

1 glass milk.
1 ounce cheese.
1 cracker

DIFFERENTIAL DIAGNOSIS OF

Gain in Weight

Gain in weight may be due to the deposition of fat or the accumulation of fluid as is frequently encountered in congestive failure or the nephropathies. Endocrine obesity is relatively rarely observed, popular opinion to the contrary notwithstanding.

The deposition of fat is a distinctly individual phenomenon. Women tend to gather fat in the region of the buttocks whereas the male is more apt to present a heavy panniculus. Certain individuals, often on a familial basis, have heavy breasts or legs. This peculiarity is transmitted, with great faithfulness, from one generation to another.

In the adult, gain in weight has not the invariably favorable connotation that prevails in the course of normal growth in infancy and childhood. Obesity predisposes to hypertension and arteriosclerosis. Retention of body fluids suggests impending difficulty as the result of backward failure or renal insufficiency.

CAUSE	DIAGNOSTIC FEATURES
Physiologic	May be racial or familial. Normal growth in children.
Hyperalimentary	With gluttony and increased caloric intake
Pregnancy	When gain exceeds 12 to 15 pounds.
Diminished Energy Output	In the sedentary and in patients confined to bed.
Retention of Salt and Water	Cardiac or nephritic edema. Look for accumulation of ascites (p. 1[illegible]21)
Psychogenic	Overeating associated with anxiety, frustration, neuroses and psychoses.
Pharmacologic	Especially in chronic alcoholism due to beer drinking.
Gastrogenous	From frequent feeding in gastric hypermotility and peptic ulcer
Hyperinsulinism	Functional manifestation in association with gluttony. Less frequently from hypersecretion associated with adenoma of pancreas. Note hypoglycemia during periods of hunger
Dyspituitarism	Frohlich's syndrome (p. 1166) with retarded obesity, fat accumulation about abdomen and hips, oligomenorrhea or amenorrhea, hypogonadism, sterility, gynecomastia, slender ankles and wrists and diminished or absent libido and potency. Get x ray of sella turcica.
Pituitary Basophilism	Cushing syndrome (p. 115[illegible]) with "buffalo head," girdle obesity, hypertension, glycosuria, linear striae of abdomen, and feminine hirsutism. Get x ray of sella turcica and region of adrenal cortex. Perform lumbar puncture and consult neurosurgeon.
Hypothyroidism	Cretinism and myxedema (p. 11[illegible]1) with thickening of the skin, loss of eyebrows, bradycardia, hypothermia and diminution in the BMR. Therapeutic response to thyroid extract.
Hypogonadism	In conjunction with the menopause, male climacteric or castration. Obesity develops with regression of secondary sex characteristics.
Adiposis Dolorosa	Dercum's disease (p. 1174) with painful lipomatous lesions.

In addition one and a half ounces of butter distributed in accordance with the patient's taste is allowed This diet contains a total of not more than 0 3 gm of calcium per day

Low Oxalate Diet

Indications —A low oxalate diet is occasionally recommended in patients with *oxaluria* (p 3680) who develop *renal calculi* (p 2311) There is considerable doubt as to whether dietary restriction has much effect on the development of renal calculi or their absorption when once formed

Foods Avoided —High oxalate foods are avoided The common foods high in oxalate content are asparagus beets green peas cabbage celery tomatoes spinach apples cranberries currants figs grapes pears plums raspberries strawberries citrus fruits in large amounts ale beer chocolate coffee pepper tea and wine

Type Diet

BREAKFAST

Stewed apricots cantaloupe banana pineapple or peach with cream and sugar
Cereal with milk or cream and sugar
Egg
Bread or toast with butter
Glass of milk

MIDDAY MEAL

Cereal beverage such as Postum
Soup if desired
Meat, fish or chicken
Potato
Vegetable except high oxalate vegetables
Salad with dressing
Simple dessert or fruit
Bread and butter
Glass of milk

SUPPER

Meat fish chicken or cheese
Potato or cereal
Vegetable with butter
Salad with dressing
Simple dessert or fruit
Bread and butter
Glass of milk

Acid Ash Diet

Indications —In patients with *phosphatic renal calculi* or *phosphaturia* and in those with permanent *bladder catheters* the administration of foods which have an acid ash is thought to prevent or minimize the production of renal calculi

Principles —In the construction of this diet emphasis is placed upon cereal bread meat and eggs at the expense of vegetables fruit and potatoes Vegetables that may be given include corn and lentils Of the dairy products American cheese eggs and a pint of milk may be given each day Any meat fish or chicken that has not been smoked or pickled is permissible Barley all kinds of bread cornmeal crackers macaroni spaghetti zwieback plain cookies and cake peanut butter peanuts walnuts and custard are permitted

Alkaline foods (see Alkaline Ash Diet) are strictly avoided

Diet and Exercise —The keystone of the treatment of simple obesity is the prescription of a well mixed *1200 calory diet* (p 669) The patient will rarely follow a routine list of suggested and forbidden foods An individual dietary should be outlined using the patient s eating habits and tastes as a guide To accomplish this the patient is asked to give his ordinary menus beginning with breakfast and then luncheon and dinner The low calory foods particularly the proteins are retained The high calory foods particularly the sugars starches and fats are eliminated

It is not at all uncommon for the patient to state that the 1200 calory diet represents more than the usual food intake A principal meal which starts with clear soup has a main protein course accompanied by two vegetables a salad a beverage and fresh fruit appears to be most generous Yet the total number of calories is low and out of proportion to the bulk

The patient should simultaneously be encouraged to indulge in gentle exercise especially *walking* and *calisthenics* Too great enthusiasm for exercise therapy particularly participation in competitive sports may defeat the purpose for which it was intended Overeating from the increase in appetite may offset any weight loss due to the increased energy output

The obese patient on a 1200 calory diet should lose at least 5 pounds in the first week This represents the burning of pure blubber During the first days of weight reduction the patient may complain of hunger asthenia and often headache The latter may be acidotic if food intake is so low that body fat alone is burned The hunger may be prevented by amphetamine It will shortly disappear when the new regime is well controlled

After the initial weight loss the weekly reduction will be reduced to 3 then 2 and later to perhaps but a single pound each week The patient must be warned against excessive dietary restriction and the employment of faddist diets such as are advertised by interested manufacturers and exploiters of foodstuffs There is no need to utilize special dietary foods So called liquid diets may be as nourishing as solid diets The important principle of dietotherapy is the arrangement of a satisfying menu on which the patient may exist indefinitely

Excessive dietary restriction and faddist diets soon become monotonous They may be followed by such intense bulimia that the famished patient regains in a few days what it has taken weeks to lose After weight has been restored to normal a maintenance diet is most easily prepared by requesting the patient to adhere to the 1200 calory diet five or six days in the week and to feast on Saturdays and/or Sundays

Restriction of Salt and Water —Salt and water restriction should be practiced in patients with threatened *circulatory failure* or *renal insufficiency* but the normal individual should handle with relative ease the average intake of salt and water Healthy patients on a reduction diet need be warned only regarding overindulgence in water and salt

There is a belief amongst the laity that drinking water with meals increases weight by augmenting the utilization of food products There is not a particle of evidence to support this dictum

Psychotherapy —Despite the simplicity of the regimen in simple obesity failure is commonly registered This is due to lack of cooperation on the

Low Sodium (Furstenberg) Diet

Indications—The low sodium regime has had some success in the treatment of *Meniere's disease* where it has been employed with ammonium chloride as an adjuvant

Principles—All foods are prepared and served without salt. Salted meat, fish or bread products are to be avoided Such vegetables as carrots spinach endive and olives which contain large amounts of salt as well as clams oysters caviar condensed milk ice cream, cheese and raisins should be strictly avoided

Twice a week the following may be used beets cauliflower celery chard horse radish lima beans, mustard, pumpkin radishes turnips turnip tops and watercress cantaloupe dried currants dates figs lime peaches strawberries muskmelon, peanuts dried cocoanut and butter milk Aside from these there are no particular restrictions

Type Diet

Breakfast

Fruit or fruit juice
Cereal such as farina oatmeal puffed rice puffed wheat with milk or cream and sugar
Eggs any style
Bread and butter with jam jelly honey or marmalade
Coffee or tea, with milk or cream and sugar

Supper or Luncheon

Cream or meat soup
Meat, fish chicken or egg dish
Potato spaghetti macaroni noodles or rice
Salad with *salt free dressing*
Cooked vegetable
Bread and butter with jam jelly honey or marmalade
Dessert, such as fruit fruit pudding cornstarch pudding gelatin tapioca pudding, custard junket, cake or cookies
Coffee or tea, with milk or cream and sugar

High Iron—High Vitamin Diet

Indications—*Malnutrition pregnancy anemias hemorrhage chronic infections* and *debilitating diseases* of long standing all suggest the need for high iron high vitamin diet

Adjuvants—In addition to dietary control it is usually wise to use iron salts and vitamin concentrates as supplements

Type Diet

Breakfast

Glass of fruit juice
Stewed or raw fruit.
Oatmeal, wheatena or any whole grain cereal
Egg
Whole wheat bread with butter
Milk or cocoa.

Midday Meal or Supper

Cream soup or vegetable soup
Liver or lean meat
Potato
Salad
Green vegetable.
Custard
Fruit, or ice cream.
Whole wheat bread with butter
Milk *or* cocoa.

rates The promiscuous use of thyroid extract by the obesity specialist who accomplishes his purpose at the expense of health cannot be too strongly condemned

Corrective and Maintenance Doses of Thyroid Extract—The patient with a low basal metabolic rate requires substitution therapy with Thyroid Extract U.S.P (p 1189) Purified preparations have no advantages over the crude extract and they are more expensive There is no need for par enteral injection since oral doses are well absorbed

The *corrective dose* of thyroid extract first is ordered Approximately 2 grains are required daily for basal rates of minus 8 to minus 15 per cent and 3 grains daily for minus 15 to minus 25 per cent After three weeks the rate is checked and the dose is altered as indicated

When the rate has been brought to normal range (minus 5 per cent to 0) the dose is discontinued for a few days and then resumed at a *maintenance level* This is most easily accomplished by omitting the drug one or two days a week

With this method significant *thyroid poisoning* should never occur Occasionally a patient may notice irritability insomnia or slight palpita tion These symptoms disappear within a few days after omission of the drug

Idiosyncrasy to thyroid is rarely seen though many patients state a susceptibility More than likely the previous difficulty was overdosage usually due to continuation of the corrective dose so that the basal rate was driven above normal True hyperthyroidism of the type of Graves syndrome cannot be produced by thyroid feeding Goitrous patients par ticularly may be completely assured of the safety of thyroid feeding where indicated and when careful observation is possible

Massage and Other Types of Friction—One of the many commercial methods of exploiting the obese is to promise removal of flesh or change in measurements by friction The friction may be applied manually by massage or with rollers or elastic garments These modalities are lucra tive but they are not therapeutic

Hydro and Physiotherapy—Cabinet baths and the like are also advo cated by those who profit by the weakness of the flesh or rather fleshy The ensuing loss of water is rapidly made up with the next inges tion of fluid

TREATMENT OF LOSS OF WEIGHT

The management of hypoalimentation like the treatment of obesity combines the technic of dietetics drug treatment and psychotherapy

High Calory Diet—A high calory dietary (p 671) is individually pre pared according to the tastes and eating habits of the patient Concen trated high calory foods are suggested to replace the bulky low calory articles of diet Sugars starches and fats (particularly butter and cream) are forced to the point of tolerance

Increased Number of Feedings—Certain patients manage a greater cal oric intake when fed three meals a day without in between feedings Others do better with frequent small feedings eating as many as six meals a day In addition to the conventional breakfast midday and evening meals these manage a mid morning feeding and a tea time and a bed time snack

Diets for the Surgical Patient

Indications—In the surgical treatment of certain diseases especially those of the alimentary tract special diets are necessary *preoperatively* and *postoperatively* In some cases the patient is allowed no nourishment by mouth for a few days after operation, the diet then slowly progresses from a liquid to a soft residue-free diet until eventually the patient may be allowed a diet that is practically normal In other cases the patient s diet will have to be carefully controlled and limited and restricted by the physician for months or years after the operation

The following lists can be varied to a certain degree according to the patient s likes and dislikes Usually however the surgeon will have his own preferences regarding diets

PREOPERATIVE DIET FOR PATIENTS WITH GASTRIC RETENTION

Approximate food value protein 50 gm calorie 2 000

Time	Food	Amount, cc
a m 8	Strained cereal with cream and sugar	00
10	Cocoa made with equal parts of milk and cream	00
12 noon	Strained cream soup	00
p m 2	Malted milk made with equal parts of milk and cream	200
4	Eggnog made with equal parts of milk and cream	200
6	Plain ice cream or gelatin with cream	200
8	Junket with cream	200

Both patient and practitioner alike must be cautioned against initial overenthusiasm in forced feeding Under these circumstances the patient's digestive tract sooner or later may rebel It is wiser to start with 2500 to 3000 calories and gradually work up to *4000 to 5000 calories* daily

Stomachics and Alcoholic Beverages —Various adjuvants are warranted in the attempt at forced feeding Any of the conventional stomachics (p 1456) may be prescribed *before the conventional* meals In the evenings there is no better appetizer than a *cocktail* The use of *wine* with the meals greatly increases the caloric intake

Carbonated beverages such as beers and ales often limit food intake because of bloat These beverages may be used at bedtime when additionally they will be soporific The practitioner should warn the patient however that the use of beer and ale at bedtime may give rise to a morning headache

Thiamine Chloride —Although the avitaminoses may be unduly stressed the clinician will frequently experience return of appetite and gain in weight when thiamine chloride is added to the diet or injected intravenously in doses of 10 to 100 mg

Psychotherapy —*With children and young folks* a reward system may be introduced for a weekly gain in weight Older adults may be required to pay a forfeit for failure to make a significant weekly weight gain

Over anxious mothers and marital partners must be warned not to be annoyingly persistent in forcing food lest the patient develop a negativism Many children eat poorly at the table because they are nagged concerning their table manners or scolded during meals for minor derelictions

Hypoglycemia Induced by Insulin —*The production of hypoglycemia by* the injection of 5 to 10 units of insulin 15 to 30 minutes before meals may produce a healthy bulimia This procedure may be utilized if the patient can be taught to give himself the hypodermic and is warned of the symptoms and dangers of overdosage (p 1241)

Correction of Abnormalities of Metabolic Rate —Increase in the metabolic rate produces loss in weight provided that the dietary intake is not *proportionately* increased The common causes of an increased metabolic rate are *hyperthyroidism* and *fever* Since either of these conditions may be masked the patient who suffers from loss of weight should have a basal metabolic rate estimation and a period of at least three days observation of the rectal temperature taken at 4 hour intervals

Patients *with increased* metabolic rates should be given small doses of iodine (p 1212) Those who suffer from Graves disease *will experience* an extraordinary gain in weight within a very few days Febrile patients whose temperature exceeds 102 F should receive antipyretic hydrotherapy or drugs since hunger contractions cease at approximately 103° F

Abstinence from Tobacco —Smoking should be forbidden Abstinence from tobacco is often sufficient to cause remarkable increase in weight

Mechanical Support —Patients who suffer from gastrovisceroptosis *should* use an *abdominal support* or the abdomen should be strapped with the adhesive plaster while the patient is in Trendelenburg position The concavity of the abdomen is filled up under the plaster with absorbent cotton

Sedatives Hypnotics and Analgesics —Anorexia that is due to nervous

POSTOPERATIVE DIETARY REGIMEN FOR PATIENTS WITH LESIONS OF THE STOMACH OR DUODENUM

Day after operation	Time	Food*	Amount
4	a m		
	8	Bland cereal gruel	100 cc
	10	Milk	100 cc.
	12 noon	Cream soup strained	100 cc
	p m		
	3	Gelatin plain with cream	100 cc
	6	Bland cereal with cream	100 cc
	8	Jello plain with cream	100 cc.
5	a m		
	8	Bland cereal with cream	150 cc
	10	Gelatin, plain with cream	1[illegible]0 cc
	12 noon	Cream soup strained	150 cc
	p m	Melba toast	½ piece
	3	Baked custard	2 tablespoonfuls
	6	Rice with cream	2 ablespoonfuls
	8	Milk and cream	1[illegible]0 cc
6	a m		
	8	Bland cereal with cream sugar	150 cc
		Egg poached or soft-cooked	1 egg
		Milk or Postum	100 cc
	10	Gelatin with cream	100 cc
	12 noon	Cream soup strained	100 cc.
	p m	Melba toast	½ piece
		Butter	½ square
		Milk or postum	100 cc.
	3	Baked custard	2 tablespoonfuls
	6	Rice with cream	2 tablespoonfuls
		Melba toast	½ piece
		Butter	½ square
		Milk or postum	100 cc.
	8	Egg nog	1[illegible]0 cc
		Further additions	
7	8 a m	Melba toast	½ piece
	12 noon	Pudding bland	2 tablespoonfuls
	6 p m	Fruit puree bland	1 tablespoonful
8	8 a m	Melba toast or rusk	½ piece
	12 noon	Potato baked or mashed	1 serving
	6 p m	Potato baked or mashed	1 serving
9	12 noon and 6 p m	Vegetable puree	1 tablespoonful
11	12 noon and 6 p m	Cottage cheese or egg dish	2 tablespoonfuls
14	12 noon	Chicken or fish	1 serving
15	8 a m	Orange juice	100 cc
		Brewers yeast	6 tablets
42		Tenderloin steak lamb chops tender roast beef tender *roast lamb crisp bacon, unstrained vegetables* †	

* See diet on p 68[illegible] for bland cereals puddings and other foods permitted and excluded

† The permissible unstrained vegetables include cooked carrots beets asparagus tips squash, string beans, and young tender peas.

The Interrelation of Plasma and Tissue Fluids.—A to-and fro passage of fluid and soluble substances is maintained between vascular compartments and the interstices of tissues This interplay occurs in the capillary bed the only portion of the vascular system permeable to blood plasma and tissue fluid Within the tissues a second equilibrium is established between intracellular and extracellular components and this too is a reversible phenomenon Nutritive elements particularly may pass from plasma into extracellular and finally into intracellular fluid Conversely excretory products and cellular secretory elements traverse the cellular membrane into the extracellular fluid and then are circulated throughout the body by passage through capillary membranes and into plasma

Fluid interchange is determined by a complexity of factors which include hydrostatic and colloid osmotic pressures lymph flow tissue tension endocrine influences neurogenic mechanisms and liver function Additionally changes may occur in the permeability of both capillary and cell membranes, these latter however are beyond the scope of the present discussion

Hydrostatic Pressure—The motive force responsible for the passage of fluid from blood into the interstices of tissues is the pressure imparted to the moving colum of blood in the capillary loops The process of the passage of fluid may be likened to filtration blood pressure acting as the filtering force and capillaries as selective filters In the capillaries of the nail fold hydrostatic pressure is 32 mm of mercury at the arterial end and 12 mm at the venous end Consideration of the factor of hydrostatic pressure is of importance in dealing with cardiac edema (p 711)

Colloid Osmotic Pressure—Osmotic pressure is a force exerted upon water molecules by substances in solution when water and an aqueous solution are separated by a membrane permeable to water but impermeable to the dissolved substance The normal capillary endothelium permits free diffusion of water electrolytes and many organic solutes of low molecular weight such as glucose urea and creatine Since it is impermeable to large protein molecules, these latter are present in higher concentration in plasma and are relatively absent from tissue fluid The protein substances exert an osmotic pressure approximating 30 mm of mercury and tend to attract water molecules a mechanism of importance in the understanding of nutritional edema associated with hypoproteinemia The osmotic pressure exerted by *colloidal constituents of the blood tends to draw fluid into the vascular bed and hence opposes* hydrostatic pressure

Osmotic relationships also are dependent on the electrolytes sodium and potassium Since the latter cannot readily traverse the semipermeable membranes it is the sodium that is concerned *mainly with osmotic pressures and hence the degree of cellular hydration Thus* administration of hypertonic saline solution or ingestion of salt water by drawing water into plasma, produces dehydration of the individual cell and the appalling thirst that occurs when shipwrecked individuals drink brine Conversely when sodium loss exceeds water loss extracellular fluid becomes hypotonic with relationship to intracellular fluid and water passes from without to within the cell As a result there occurs simultaneously a dehydration of extracellular fluid and a water intoxication or edema within the cell

Colloid and hydrostatic pressures may be cumulative or antagonistic In the latter circumstance one agency tends to force fluid out of the blood while the other draws it into the capillaries The resultant is determined by relative pressure relationships Normally at the arterial end fluid is forced out while at the venous end it is drawn back

Lymph Flow—The lymphatics are concerned with return to the blood stream of tissue fluid as well as the protein moiety When their function is impaired plasma protein is retained in extracellular fluid and intravascular osmotic pressure is reduced favoring edema

Tissue Tension—Outside of the capillaries the tension of the interstitial tissues tends to counteract hydrostatic pressure and oppose the filtration process This is most marked where the tissues are unyielding as in bone Lax subcutaneous tissues offer little resistance and afford a potential reservoir for fluid accumulation

Endocrine Influence—The amount and distribution of body water and electrolytes ("the building blocks of edema) also are determined by the activity of certain hormones These include posterior pituitary antidiuretic factor thyroid adrenal cortex corpus luteum (progesterone) and other hormonal factors as yet unsuspected

Posterior pituitary antidiuretic factor regulates the reabsorption of water by the kidney (cells of Henle's loop) and contributes to the maintenance of the volume of body fluids By an action on capillary endothelium this factor may also affect the passage of water and salt between tissue spaces and capillary bed In the presence of an excessive water intake the administration of posterior pituitary extract causes temporary retention of water in tissue

DIET FOLLOWING SIMPLE CHOLECYSTECTOMY AFTER DISMISSAL FROM HOSPITAL

Breakfast	
Fruit	1 serving
Cereal	1 serving
Toast	1 slice
Butter	½ square
Milk	1 glass
Cream	2 tablespoonfuls
Coffee if desired	
Noon Meal	
Soup (cream or vegetable)	1 cup
Meat or fish (lean)	1 serving
Potato or substitute	1 serving
Vegetable hot or as salad	1 serving
Bread	1 slice
Butter	½ square
Dessert fruit	1 serving
Milk	1 glass
Tea or coffee if desired	
Evening Meal	
Meat or fish (lean)	1 serving
Potato or substitute	1 serving
Vegetable	1 serving
Salad fruit or vegetable	1 serving
Bread	1 slice
Butter	½ square
Dessert fruit	1 serving
Tea or coffee if desired	

Foods Excluded—Fried foods of all kinds salad dressings made with oil or containing much cream pies rich cakes pastries and desserts fat meats gravies eggs (as far as practical) nut chocolate vegetables such as cabbage turnips kohlrabi cauliflower cucumbers Brussels sprouts onions rutabagas dried beans and radishes.

PREOPERATIVE DIET FOR PATIENTS WITH DISEASES OF THE COLON

Residue free Diet

Approximate food value carbohydrate 4[illegible]0 gm protein 10 gm fat 75 gm calories 2[illegible]00

Breakfast	
Fruit juice (with 25 gm dextrin mixture)	1 glass
Cream of wheat	½ cup
Cream 40 per cent butter fat	½ cup
Toast melba	2 pieces
Butter	1½ squares
Jelly	1 tablespoonful
Sugar as desired	
Coffee if desired	
Noon Meal	
Fruit juice (with 25 gm dextrin mixture)	1 glass
Steamed rice macaroni spaghetti noodles	½ cup
Toast melba	2 pieces
Butter	1½ squares
Jelly	1 tablespoonful
Cream 40 per cent butter fat	1 tablespoonful
Sugar as desired	
Tea or coffee if desired	
Evening Meal	
Fruit juice (with 25 gm dextrin mixture)	1 glass
Steamed rice macaroni sphagetti noodles	½ cup
Toast melba	2 pieces
Butter	1½ squares
Jelly	1 tablespoonful
Cream 40 per cent butter fat	1 tablespoonful
Sugar as desired	
Tea or coffee if desired	

have a greater appeal than those that are flat When fluid loss is due to vomiting the chloride ion must be furnished by the simple expedient of giving table salt *In diarrheal conditions it is better to supply alkali in the* form of bicarbonate of soda

Those patients who are unable to ingest fluid may be given a *proctoclysis* using water physiologic saline or Ringer s solution If neither oral nor rectal routes of administration can be employed fluid may be administered through the *duodenal* or *Miller Abbott tube* (p 1752)

If enteral methods prove unsuccessful fluids are given parenterally by *hypodermoclysis* (p 3771) or the method of the *intravenous drip* (p 3775) *An infusate of whole blood is preferred in conditions of hemorrhage plasma* is employed in shock the vomiting patient receives physiologic saline solution but with diarrhea it is better to use Ringer s solution or sodium r lactate

In the conduct of his therapy, the practitioner must avoid the pitfalls of using excessive concentrations of dextrose an undue bulk of fluid or inordinate amounts of sodium chloride Hypertonic dextrose in concentrations in excess of 5 per cent abstracts water from tissues and increases *cellular dehydration hence its use is not advisable in the presence of an* hydremia The production of the bulk reaction by the continuous intravenous drip especially in patients with limited cardiac reserve may result when an excess of 4 to 5 liters are daily infused Again with the intravenous drip an infusion of physiologic saline solution which contains 9 gm of salt to the liter may result in hyperchloridemia and edema if more than 2 liters (18 gm of NaCl) are given within the course of twenty four hours It should therefore be an unwritten rule to replace the saline solution *with triple distilled water after 1500 to 2000 cc have been introduced* With the drip method there need be no fear that water will produce hemolysis of red cells

During the course of the intravenous drip oral hygiene must be carefully practiced to avoid the complication of a non suppurative parotitis The flow of saliva is encouraged by the use of chewing gum Oral fluids are given as soon as is practicable

HYPERHYDRATION

(*Bulk Reaction Water Intoxication Hyperhydremia*)

Hyperhydration the opposite of dehydration occurs when excessive amounts of water are introduced orally or intravenously and as a result of impaired elimination most particularly with oliguria or anuria

Clinical Manifestations—With normal excretory conditions water intoxication does not occur in clinical medicine However terrorists have employed the water cure as an exquisite and inexpensive method of torture The syndrome of hyperhydration includes fall in temperature vomiting convulsions and death

Under clinical conditions hyperhydremia occasionally occurs with the continuous *intravenous drip The bulk reaction may accompany* the daily introduction of several liters of fluid and is more prone to occur in those with diminished cardiac reserve The bulk reaction is manifest by fall in systolic pressure rise in diastolic pre sure and a markedly diminished pulse pressure The patient shows manifestations of subcutaneous or pul

DIET FOR PATIENTS WITH COLONIC STOMA

Breakfast

Fruit or fruit juice	1 serving
Cereal	1 serving
Bacon	1-2 strips
Egg	1
Bread	1 slice
Butter	1 square
Cream	½ cup
Beverage as desired	

Noon Meal

Meat, cheese or egg	1 serving
Potato or substitute	1 serving
Vegetable	1 serving
Bread	1 slice
Butter	1 square
Fruit	1 serving
Milk	1 glass
Cream if desired	2 tablespoonfuls
Beverage as desired	

Evening Meal

Soup	1 serving
Meat	1 serving
Gravy if desired	
Potato	1 serving
Vegetable	1 serving
Salad (dressing if desired)	1 serving
Bread	1 slice
Butter	1 square
Dessert (other than fruit)	1 serving
Milk	1 glass
Cream if desired	2 tablespoonfuls
Beverage as desired	

Foods Permitted—Fruit, raw ripe banana, grapefruit or orange sections or juice, lemon juice avocado Fruit, cooked or canned applesauce baked apple without skin apricots peaches pears cherries strained cranberries Cereal cornmeal farina maltomeal cream of wheat fine oatmeal cornflakes puffed rice puffed wheat rice flakes rice krispies Bread white light rye without seeds cornbread biscuits muffins popovers, rolls waffles griddle cakes doughnuts Cheese American cottage cream Swiss Vegetables raw lettuce tomato without skin or seeds tender celery hearts Vegetables cooked or canned asparagus beets, carrots wax beans green beans small peas potatoes squash pumpkins corn puree Potato substitutes rice noodles macaroni spaghetti Desserts bland (without fruits nuts or cocoa nut) plain cake and cookies Jello and gelatin desserts plain puddings such as rice bread, tapioca or cornstarch ice cream ices sherbets pie made of allowed fruits

Foods Excluded—Bran and all whole grain cereals and breads fruits and vegetables with fiber many seeds or tough skin such as melons mushrooms pickles cucumbers, and berries, gas forming foods such as onions the cabbage family dried or fresh beans such as lima and navy beans radishes green and red peppers

and scrotum are usually involved and edema of the skin may disappear with persistence of ascites and hydrothorax The joints are rarely involved but edema of the gastro intestinal tract may impair intestinal absorption of protein and cause bouts of diarrhea

The edema fluid is usually opalescent and has a specific gravity below 1 015 The protein content is less than 0 1 per cent in fluid obtained from the skin while it is somewhat higher (0 28 per cent) in ascitic fluid and pleural effusions The urine is usually scant especially while edema is forming The specific gravity is high since renal function is unimpaired The cardinal feature is the albuminuria which may amount to 26 gm daily Doubly refractile lipoids (cholesterol esters) are present in the urinary sediment and as much as 41 mg of cholesterol have been excreted daily The source of these lipoids may be the renal epithelium in which they are deposited in large quantity or the lipoidemia Hematuria may be present but is usually slight

Analysis of the blood reveals a serum albumin concentration below 2.5 gm per cent and *inversion of the albumin-globulin ratio* Fibrinogen and globulin contents of plasma are sometimes increased there is a striking increase in blood fat especially *cholesterol* The plasma has a characteristic milky appearance Red corpuscles sediment quickly and blood calcium is low due to reduction in the non ionized fraction bound to protein

The basal metabolic rate is low and the patient is relatively insensitive to large doses of thyroid The cause of this refractoriness is unknown but may be related to a compensatory reduction in metabolism due to edema. Patients with nephrotic edema are susceptible to pneumococcal infections and not uncommonly succumb to pneumococcal peritonitis

The nephrotic syndrome presents a number of extremely interesting exceptions to current hypotheses of the pathogenesis of edema Infection occasionally provokes a profuse and lasting diuresis similar results may at times be obtained with large doses of potassium salts or the administration of pituitary antidiuretic factor An antidiuretic factor of undetermined origin may be demonstrated in the urine in some cases and occasionally spontaneous diuresis will occur with little or no change in the plasma protein level

Nephrotic Stage of Chronic Glomerulonephritis—Edema of the type observed in the nephrotic syndrome often is encountered in the course of chronic glomerulonephritis Protracted massive albuminuria leads to hypoproteinemia diminished colloid osmotic pressure in plasma excessive transudation and edema The clinical picture may be indistinguishable from chronic nephrosis Many students of renal disease believe the conditions are identical The chemical findings in blood and urine are similar but anemia is apt to be more common in the nephritic who may also exhibit an elevation of blood pressure Widespread capillary injury may lead to increase in capillary permeability cardiac failure and capillary anoxemia further provoking edema

Nephrotic Stage of Amyloidosis—Renal amyloidosis which produces massive albuminuria also favors the development of a nephrotic type of edema The clinical and chemical features are similar to those present in the previously described disorders Attempts to differentiate amyloid disease by the Congo Red test are likely to be futile because of the rapid

the trend is progressive specialist consultation is advisable X rays are taken of the sella turcica the ophthalmologist plots the visual fields and examines the fundus and the findings require review by the neurosurgeon In the presence of a demonstrable or suspected tumor, operative and roentgen therapy may be indicated (p 1177)

Treatment of Decreased Growth —The presence of infantilism or dwarfism is of sufficient significance so that an extensive diagnostic survey is indicated A complete physical examination is performed to uncover any

DIFFERENTIAL DIAGNOSIS OF

Increased Growth

Anxious parents not infrequently bring children for consultation as the result of abnormally rapid growth Many young ters attain adult size as early as the twelfth year Increased stature is rarely accompanied by a proportionate gain in weight, so that the child appears awkward, frail and lean, and may have deep circles under the eyes It is common belief amongst the laity that excessive growth is unhealthy and may result in diminished resistance particularly weakening of the heart De pite these fears examination reveals no significant abnormality and the hemogram is surprisingly normal The child rarely suffers from any disturbance beyond expected disabilities of puberty and adolescence The practitioner confidently may assure the parents that increased stature is a physiologic variant since pathologic alterations in height are sufficiently rare to be counted as medical curiosities. Assurance may also be given that there is no justification for fearing heart strain. Normal exercise may be encouraged and there is no need for gland treatments which have much greater potential for harm than for benefit

CAUSE	DIAGNOSTIC FEATURES
Physiologic Variants	Usually familial or racial
Prepuberal Hyperpituitarism	In giantism (p 1155) growth stimulus occurs before epiphyses have joined. May be associated with eunuchoid or acromegaloid features and disturbances of vision. Get x ray of sella turcica (p 1152)
Postpuberal Hyperpituitarism	Acromegaly (p 1177) in which growth stimulus occurs after junction of epiphyses Marked changes in the short and flat bones with prognathous enlargement of feet and hands and genital disturbances Note enlargement or destruction of sella turcica (p 1177) Contraction and defects in visual fields (p 1158) with expanding pituitary tumors (p 1175)
Hyperpinealism	Macrogenitosomia praecox (p 1185) with marked sexual hyperdevelopment.

systemic disturbance that might be responsible for an example of secondary hypopituitarism (p 1164) X rays of the sella turcica may reveal abnormalities that suggest the presence of a neoplasm accessible to surgery or roentgentherapy (p 1177) A diminution in the basal metabolic rate arouses the hope that the child may be suffering from the cretinous type of dwarfism amenable to therapy with thyroid extract (p 1189) Growth disturbances due to dietary rickets may yield to the administration of vitamin D but the prognosis of renal rickets is utterly discouraging unless

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there is present some surgical uropathy that may be corrected by operative procedure (p 2234)

Lacking a more hopeful approach, glandular therapy may be attempted with anterior pituitary growth hormone supplemented by injections of estrogen and/or androgen Since the use of these potent products is still in the experimental phase consultation with an internist especially interested in endocrinology is recommended The greatest promise of substitution therapy is afforded in dyspituitarism associated with the adiposogenital syndrome of Frohlich (p 1166)

DIFFERENTIAL DIAGNOSIS OF

Diminution in Adult Size

Diminution in adult size most often results from bowing of the spine as is particularly noted in the aged Less frequently the shrinkage is the result of osseous disease

CAUSE	DIAGNOSTIC FEATURES
Senility	Usually a progressively increasing kyphosis
Osteitis Deformans	Paget s disease of bone usually encountered in middle years Bending and bowing of long bones, particularly tibias, with progressive enlargement of skull (p 2879) Note thickening of skull with cotton wool appearance by x ray (p 2881)
Osteomalacia	Usually encountered in improperly nourished pregnant women (p 2853) Marked kyphoscoliosis muscle weakness pelvic deformity and generalized osteoporosis Try therapeutic response to vitamin D and calcium
Paralysis Agitans	Parkinson s disease with rigidity weakness, intention tremor propulsion gait, mask like facies and progressive kyphosis
Osteoarthrosis of the Spine	Spondylitis deformans with progressive rigidity of spine atrophy of intervertebral discs, hyperostoses and muscle atrophy (p 2859)
Tuberculosis of Spine	Destruction of vertebral bodies with abscess formation in soft tissues (Pott s disease) May result in local deformity with gibbus (humpback) Get x ray of spine temperature record and sedimentation rate

Treatment of Diminution in Adult Size.—The treatment of diminution in adult size is most unsatisfactory There is prospect of correction of the fundamental difficulty only in osteomalacia when large doses of vitamin D with calcium may be administered Under other circumstances the best that can be accomplished is symptomatic relief through exercise and mechanical support

DISTURBANCES IN WEIGHT

Disturbances in body weight are most often due to deviations in the metabolism of water and fat Rapid alterations usually result from dehydration or the accumulation of edema fluid More gradual fluctuations occur when adipose tissue is burned or deposited

Impaired Protein Formation
Hepatic cirrhosis
Chronic nephrosis

Nutritional edema differs from the nephrotic syndrome in many important respects the *hypoproteinemia* is rarely as pronounced the *urine* may show no abnormality there is no elevation of *blood cholesterol* and *anemia is usually present as the result of the underlying disorder*

Treatment—The treatment of nutritional edema is most satisfactory when the disturbance is dependent upon an inadequate dietary intake Under those circumstances the high protein diet is supplemented by the addition of the available vitamins particularly of B complex In the presence of hookworm disease anthelmintics (p 1898) are employed to eradicate the fundamental difficulty Transfusion of whole blood is a most valuable temporary expedient It may be followed by a remarkable diuresis

EDEMA DUE TO INCREASE IN HYDROSTATIC PRESSURE
(*Venostasis*)

The pressure of the blood in the capillaries is determined by the force of the heart (*vis a tergo*) and the efficiency of the mechanisms concerned with adequate venous return Impairment of either or both of these factors produces venostasis and engorgement in the capillary bed Under these circumstances there is general increase in hydrostatic pressure and diminished reabsorption of fluid at the venous end of the capillary loop Slowing of the capillary stream results in a greater utilization of oxygen and eventually leads to tissue anoxemia Local anoxemia in turn produces capillary dilatation and increase in cell permeability These factors encourage the passage of protein through the capillary wall which further decreases effective colloid osmotic pressure

The end result of the interaction of these functional derangements is edema The distribution may be general or local depending on the extent of the circulatory disturbance

Postural Edema—Transient edema is not uncommonly encountered in the normal individual who must maintain the erect posture for a long period The swelling appears in the lower extremities and usually involves the dorsum of feet ankles and legs The accumulation of fluid results from excessive transudation of fluid into the tissue spaces of dependent parts There also may be obscure disturbances in the mechanics of lymph flow due to changes in muscle tone

Treatment—Rest in the recumbent position causes postural edema to disappear If it recurs repeatedly elastic stockings are advised Prevention is accomplished by muscle contractions or exercise at regular intervals during the period of standing

Peripheral Vascular Obstruction—Mechanical obstruction of veins causes venous stasis with the development of local anoxemia and edema If obstruction is acute and complete there may be extensive hemorrhagic manifestations and infarction of tissue Mechanical venous obstruction is usually incomplete and due to localized venous pathology for example thrombophlebitis carcinomatous infiltration and compression Some of the common clinical types are seen in the superior and inferior venae cavae

Hyperalimentary Obesity—Obesity resulting from overeating presents a combined psychiatric and metabolic problem Most often the gluttonous patient will deny overeating and resent the accusation To approximate the actual caloric intake a complete dietary must be recorded over a period of several days The alimentary error may be a general state of overeating or it may consist of excessive indulgence with or between meals in high calory foods such as whipped cream olive oil candy bars sodas or fruit drinks The food intake may be within normal limits but added calories may be derived from alcohol in the form of beer wine gin or whisky At times the dietary intake is unchanged but energy output is diminished This last is particularly noted in boys fresh from school or college where they have indulged in athletics With later sedentary work they have minimum muscular activity and become flabby and heavy

Hyperalimentation is frequently a character defect rather than a metabolic error The patient becomes restless anxious or frustrated and can no more refrain from eating high calory foods than the alcoholic can refuse the cup that cheers As a metabolic response to the psychologic derangement hyperinsulinism is produced The resultant hypoglycemia acts as a stimulus to appetite and hunger returns long before the time for the next scheduled meal There is established a vicious psychosomatic cycle which can be overcome only by the exercise of tremendous will power The psychogenic aspects of obesity require consideration in therapy as well as diagnosis

Obesity in Pregnancy—Excessive gain in weight should not be tolerated or encouraged during pregnancy There is no reason for the gravid woman to gain more than 12 to 15 pounds during her child bearing period Women who gain an excessive amount of weight during pregnancy are faced with a difficult problem after the birth of the baby They may remain obese and suffer the consequences both medically and esthetically If they decide to go in for vigorous weight reduction they are apt to become flabby and lose their attractiveness It is far simpler and more satisfactory to prevent gain in weight by use of a low calory diet which if essential amino acids minerals and vitamins are provided in adequate amounts does not reduce the size of the baby

Plumpness—The patient who is normally plump often presents a difficul problem to the practitioner Women particularly insist upon weight reduction so that they may effect a fashionable contour and wear modish clothes Each patient has what pugilists recognize as fighting weight Professional athletes learn that training that is too fine reduces strength below optimum Normally plump women must be warned that excessive weight reduction cannot be accomplished without diminution in strength and resistance They must be prevented from accomplishing an unphysiologic purpose by faddist diets and the unjustified use of thyroid extract amphetamine sulfate and dinitrophenol whether taken without prescription or with the sanction of the obesity specialist

TREATMENT OF OBESITY

The treatment of simple obesity resulting from hyperalimentation and decreased energy output is easily outlined Cooperation however is rarely obtained

vored by pre-existent venostasis and infection of the vein wall About 90 per cent of venous thromboses occur in the veins of the lower extremities Spontaneous saphenous vein thrombosis occurs in males as a result of a patchy or tubular phlebitis The resultant edema is slight Saphenous thrombosis may be an early symptom of thrombo angiitis obliterans

Thrombophlebitis of deep and superficial leg veins is commonly encountered Deep vein thrombosis produces a rapid swelling of the leg which becomes white and hard producing the milk leg or phlegmasia alba dolens In all thrombophlebitides there is an associated factor of lymphatic obstruction due to involvement of perivenous lymphatics

Thrombosis of the axillary vein after a radical dissection of the axilla is the commonest form of venous occlusion encountered in the upper extremity There is associated lymphatic obstruction by infection or carcinomatous infiltration of the regional lymph nodes Axillary vein thrombosis produces a brawny edema of the entire arm

Arteriovenous Fistula—Local increase in hydrostatic pressure is produced when there is a direct communication between artery and vein The shunting of arterial blood into veins raises venous and capillary pressures producing dilatation of the small vessel bed transudation and edema The shunts are usually the result of trauma and are most commonly encountered in the lower extremity (popliteal area) Extensive changes in circulatory dynamics may occur if the communication is sufficiently large There is compensatory increase in blood volume and the increased blood mass may cause cardiac dilatation with failure of the heart

Communication between the internal carotid artery and the cavernous sinus produces pulsating exophthalmos with extensive edema of ocular and bulbar conjunctivae intense engorgement of the retinal veins and numerous retinal hemorrhages

Treatment—The treatment of the edema that results from mechanical obstruction is primarily concerned with the attempt to relieve the factor of compression by surgical means such as excision of a tumor or ligation of an arteriovenous shunt In the extremities bandaging or elastic stockings may be employed for greater comfort

EDEMA IN BACKWARD FAILURE

Backward failure is discussed in detail in the section devoted to Circulatory Disease (p 941) The localization and extent of the cardiac inefficiency depend on involvement of one or both ventricles When the *left ventricle* is incompetent there is stasis of blood in pulmonary capillaries with transudation of fluid into pulmonary alveoli The onset of pulmonary edema may be acute giving rise to paroxysms of cardiac asthma (paroxysmal dyspnea) or it may be chronic producing less intense interference with respiration The presence of fluid in pulmonary alveoli interferes with free diffusion of gases between blood and alveolar air and produces anoxemia which further alters capillary permeability

Failure of the *right ventricle* causes engorgement of the systemic capillary bed The resultant edema is generalized but is greater in dependent areas due to the influence of gravity It appears first in the legs or in recumbent patients over sacrum and lower abdomen The liver is enlarged and may pulsate There may be massive ascites which hinders respiratory

part of the patient and failure of the practitioner to recognize the psychological factors involved

For this reason the wise practitioner must devise psychological devices to offset by rewards and forfeits the weakness of human flesh Children and young adults may be paid off for their weekly loss of weight Older patients should be required to pay a forfeit to the local community chest if there is no significant weight loss each week If weight loss fails to occur despite cooperation, a hypothyroid type of obesity is suspected

Successful obesity specialists accomplish results where the average practitioner fails by demanding large fees in advance and requiring the patient to report daily for the menu The latter usually proves to be the conventional 1200 calory mixed diet with certain culinary trimmings To the surprise and consternation of the legitimate practitioner the specialist" may succeed where the routinist fails The difference in result may be credited to the psychological factor that the patient or his relative felt it essential to obtain value for money expended

Alimentary Drugs —Potent drugs are often employed by the obesity specialist whose interest is more in the weight scale and the pocketbook than in the health of his patient Most of these drugs are employed for the purpose of curbing the appetite *Belladonna* and the *atropine* derivatives are used to effect dryness of the mouth and thus produce anorexia *Digitalis* and *ipecac* are given in sufficient dosage to produce nausea These practices are to be discouraged

Amphetamine sulfate (*benzedrine*) produces a striking anorexia when given in the exceedingly small dosage of 2 5 to 5 mg before breakfast and at noon time Larger dosage is apt to produce insomnia Of the drugs that tend to discourage hyperalimentation only the use of amphetamine is advised

Diuretic Drugs —Because of the striking loss in weight that accompanies diuresis in the water logged patients the diuretic drugs have also been employed in the treatment of simple obesity This practice is mentioned only to be condemned While it is true that a striking loss of weight may be recorded on the day of administration isotonicity will shortly be restored Water is again retained and the lost weight is regained

Drugs Intended to Increase Energy Metabolism —The basal metabolic rate may be increased above the normal by the administration of *thyroid extract* and/or *dinitrophenol* or *dinitrocresol* Though thyroid extract is of great utility in the lowered basal states the prescription of the latter two preparations is distinctly *hazardous* and is rigorously condemned These drugs may cause hepatitis blood dyscrasia and a late development of cataractous changes in the lens resulting in blindness The latter is particularly insidious and may not occur until long after the cessation of the drug

The problem often arises as to the wisdom of giving thyroid extract to raise the basal metabolic rate above normal The only circumstances under which this seems permissible is the instance of those patients who have religiously followed the low calory diet without effecting any weight reduction If the physician is convinced of the integrity of his patient he may conscientiously include thyroid in the regimen provided that the patient will report regularly for observations of pulse and basal metabolic

tional activity of capillary endothelium edema from this cause is encountered most frequently

Histamine Wheal—Intradermal injection of histamine produces local increases in capillary permeability with the formation of a wheal in the affected area If the colloidal dye (Congo red) is injected intravenously at the same time dye appears only in the area of the histamine wheal indicating that the local capillary endothelium here is unusually permeable to large molecules

Allergic Edema—Interaction of antigen and antibody in susceptible individuals produces widespread capillary injury leading to increase in capillary permeability and edema This may be due to direct action on endothelial cells or it may be the result of formation of a *histamine like substance* in the body

Clinically the factors that determine the localization of allergic edema are poorly understood but almost any tissue and body area may be involved Allergic edema may take the form of urticarial wheals or an angioneurotic edema localized to the face particularly the periorbital skin or it may affect the mucosa of the respiratory tract producing swelling of laryngeal tissues and bronchial mucous membrane Edema of the gastrointestinal tract may cause epigastric distress and if the biliary ducts are involved obstructive icterus may be encountered

Treatment—The symptomatic treatment of allergic edema consists primarily in the local or systemic use of adrenergic drugs (p 3877) Epinephrine in concentrations of 1 1000 to 1 100 may be used by topical application or by spray particularly in the allergic edemas of the upper respiratory passages Epinephrine (1 1000) is injected for its systemic effect The soluble calcium salts seem to offer some measure of relief when given intramuscularly or intravenously The use of the potassium salts and ascorbic acid has not been marked by any signal success despite preliminary enthusiastic claims In a dire emergency as in edema of the larynx it may be necessary to perform scarification when drug therapy fails

Serum Sickness—About a week after the administration of horse serum evidences of widespread capillary injury with edema formation may appear There may be extensive urticaria edema of the larynx hydroarthrosis and manifestations of gastro intestinal involvement Damage to the glomerular capillaries results in hematuria and albuminuria Epinephrine and calcium salts afford symptomatic relief (p 3877)

Inflammatory Edema—Edema is a cardinal manifestation of the inflammatory response Inflammation the tissue reaction to a noxious agent is a purposive phenomenon whose aim is to localize and remove the irritant The inflammatory process involves local capillary dilatation increase in blood flow to the affected area increase in capillary permeability with excessive transudation and edema formation and migration of phagocytes These vascular phenomena are responsible for the local redness heat and swelling of the inflammatory reaction which may arise from the formation of a *histamine like* substance as a result of an initial injury to tissue cells Capillary and venous thrombosis and lymphatic obstruction contribute to the formation of edema during inflammation

Inflammatory edema does not require treatment unless it has caused

DIFFERENTIAL DIAGNOSIS OF

Loss of Weight

Loss of weight is an arresting symptom most particularly when it progresses to the stages of emaciation and cachexia It is an ominous manifestation during periods of normal growth in infancy and childhood It has promise of beneficence during deliberate reduction in obesity or when a negative water balance is established in the edematous

CAUSE	DIAGNOSTIC FEATURES
Physiologic	Racial or familial During senility and following pregnancy
Hypo-alimentation	Fasting Due to edentia and other oral disturbances As the result of a low calory or unbalanced diet. In association with excessive smoking Prescribe high calory diet (p 671)
Negative Water Balance	Dehydration diet, diaphoresis diuresis vomiting diarrhea or paracentesis of chest or abdomen
Increased Energy Output	Exercise and heavy manual labor
Increased Catabolism	With elevation of the BMR during fever and leukemia In prolonged infections and the malignancies Get temperature record and hemogram (p 3692)
Gastrogenous and Enterogenous	As the result of achylia gastrovisceroptosis nausea vomiting diarrhea or absence of pancreatic ferment (pancreatic infantilism) Barium x ray and stool examination (p 3727)
Psychogenic	From anxiety or pain In situational difficulties, neuroses psychoses and anorexia nervosa (p 1768)
Infectious	As the result of the combination of increased metabolic rate increased catabolism and hypo-alimentation. Prescribe high calory diet (p 671)
Hyperthyroidism	Tachycardia tremor goiter and elevation of basal metabolic rate (p 1206) Therapeutic response to iodide (p 1213)
Hyperinsulinism	Diabetes mellitus (p 1246) With hyperglycemia and glycosuria Advise dietary regulation with insulin (p 1255) if required
Adrenal Cortical Deficiency	Addison s disease (p 1271) With asthenia hypotension and pigmentations of mucosa and skin Note responses to cortical extract and sodium (p 1276)
Anterior Pituitary Deficiency	In Simmonds disease (p 1169) with profound asthenia emaciation, amenorrhea and marked depression of the basal metabolic rate. Get x ray of sella turcica
Pharmacologic	In alcoholism and drug addiction As the result of the administration of digitalis and diuretics in the edematous. From the use of thyroid extract, amphetamine sulfate and dinitrophenol in the obese

bital edema which is similar to that seen in patients with acute nephritis There is usually extreme edema of the subconjunctival tissues and well marked chemosis The capillary damage is produced by toxic products arising from the presence of the parasite

Vitamin C Deficiency—A dietary deficiency of vitamin C leads to increased fragility and permeability of capillaries The defect results from failure to elaborate intercellular substances which act to obliterate the interstices between endothelial cells Hemorrhages follow slight trauma particularly in the periosteal tissues of infants along the gingival margins in joint spaces and subperitoneal tissues Rarely an extensive pericardial effusion may be encountered in scorbutic patients Vitamin C deficiency responds specifically to the administration of cevitamic or ascorbic acid (p 627)

Burns—In extensive burns damage to widespread areas of epithelium often produces extensive capillary damage The loss of large quantities of plasma at the injured site contributes to the edematous tendency by decreasing plasma colloid osmotic pressure The presence of edema in the burned patient is an urgent indication for plasma infusion (p 3778)

Weeping Skin Lesions—Generalized edema may occur in patients especially children with extensive eczematoid or infectious skin lesions There may be widespread increase in capillary permeability and loss of plasma from the site of the lesions as in the case of extensive burns

EDEMA DUE TO THE PRIMARY RETENTION OF HYDROPIGENIC SUBSTANCES (WATER AND SODIUM CHLORIDE)

An excessive quantity of water and sodium chloride the building blocks of edema may be retained in the body as a result of the action of hormones which affect the distribution in the body and the renal excretion of these substances Hydropigenic edema occurs from the action of endogenous hormonal factors or as a result of hormonal replacement therapy

Menstrual Edema—For several days prior to an expected menstrual period many women experience sudden increase in weight of 3 to 4 pounds and moderate edema of fingers feet breasts and face These changes result from retention of water and sodium chloride coincident with the peak activity of the corpus luteum hormone Metabolic studies reveal a diminished urinary excretion of sodium chloride and water during the period of edema formation Similar results may be obtained in normal subjects with injections of the corpus luteum hormone (progesterone)

The treatment of premenstrual edema is accomplished by oral administration of ammonium salts (p 2486) and by the use of androgen (p 2401)

Desoxycorticosterone Edema—Desoxycorticosterone a steroid hormone of the adrenal cortex increases the reabsorption of sodium and chloride by the renal tubules Administration of the hormone to normal individuals may be attended by mild degrees of edema usually in the loose periorbital skin pretibially and over the sacrum In patients with Addison s disease treatment with desoxycorticosterone acetate produces a more striking retention of sodium chloride and water greater increase in plasma volume and body weight and obvious edema An additional factor contributing to edema formation in the Addisonian is myocardial weakness and conges

ness worry insomnia or pain must be symptomatically treated with sedatives hypnotics and analgesics

Miscellany —Anorexia may be caused by abdominal discomfort or constipation It may result from situational difficulties bad cooking slovenly preparation and serving of food unpleasant or incompatible table companions Nasal obstruction and nasal discharge are frequent causes of anorexia Local treatment directed at the rhinological difficulty may result in improved appetite and gain in weight

DISTURBANCES OF BODY FLUIDS

Clinical disturbances in the amount and distribution of body fluids are at once simple and difficult of comprehension They are readily interpreted when dehydration follows intractable vomiting or diarrhea or when a local edema of the ankle results from stasis in varicose veins The more complicated derangements, however, may involve alterations in electrolytes changes in body proteins and altered permeability of capillary membranes

Because of the diversity of factors concerned with shifts in body fluid rational treatment of any presenting derangement depends upon a clear understanding of the deranged physiologic mechanism

PHYSIOLOGY

Circulating Fluids —The vascular channels contain a mass of circulating fluid that approximates 72 to 100 cc per kg of body weight Whole blood volume is indirectly calculated by injecting into the blood stream a known amount of a slowly excreted dye such as Congo red and determining its dilution

Whole blood is composed of red blood cell components and plasma The former are enumerated in the counting chamber variants include anemia and polycythemia conditions more properly discussed in the section dealing with Disturbances of the Blood (p 1035) Disturbances of body fluids are concerned most with abnormalities of plasma which normally constitute 43 to 59 cc per kg of body weight. The maintenance of the quantity of blood plasma is dependent upon a wide variety of physical and chemical mechanisms for whereas cellular elements of circulating blood remain fairly well confined to vascular channels plasma is capable of modification through semipermeable capillary membranes

Tissue Fluids —The tissue fluids which closely resemble plasma and lymph in composition may be intracellular or extracellular Extracellular or free fluid is separated on the one side from circulating fluid by the capillary membrane and on the other side from cytoplasm by the cellular membranes Between intracellular fluid and plasma are the semipermeable membranes of capillary and cell A constant interchange occurs between extracellular and intracellular fluids and between extracellular fluid and plasma The systems are in a constant state of flux and the character and quantity of each is dependent upon alterations that occur in the other two

The simpler clinical derangements of body fluids are purely quantitative The patient who is deprived of normal water intake naturally suffers from a process of desiccation or dehydration and the unfortunate individual who is compelled to take the water cure and drink inordinate amounts of fluid or who is smothered by the intravenous injection of excessive amounts of fluid is afflicted with the syndrome of hyperhydration

Qualitative changes in body fluids are much more subtle and their elucidation requires review of the factors concerned in the interchange of fluid between plasma and tissue elements The necessity for clear understanding is best illustrated by the conditions that prevail in shock and in the dilemma of shipwrecked sailors who find water water everywhere nor any drop to drink In shock due to increased permeability of capillaries plasma volume falls while the quantity of extracellular fluid increases The shipwrecked victim who drinks seawater may increase the amount of his plasma and extracellular fluid but he produces dehydration and increased thirst of his cells due to loss of intracellular water The elucidation of these mechanisms will become clearer after the review of physiological circumstances

DIFFERENTIAL DIAGNOSIS OF

Generalized Edema (Anasarca)

CAUSE	DIAGNOSTIC FEATURES
Lipoid Nephrosis	Marked albuminuria. Serum protein below 5 gm. serum albumin less than 2 5 gm. per cent. Reversal of albumin-globulin ratio Urine specific gravity high Doubly refractile lipoids in urinary sediment (p 3680) Marked hypercholesterinemia (p 736) Lowered BMR Favorable response to high protein diet and thyroid.
Nephrotic Stage of Chronic Glomerulonephritis	Same as lipoid nephrosis but urine specific gravity apt to be low with casts and red blood cells in sediment. Somewhat favorable response to high protein diet (p 674)
Nephrotic Stage of Amyloidosis	As above but hepatomegaly and splenomegaly with amyloid infiltration of these organs Congo red test (p 7)
Diabetic Nephrosis	As above but with hyperglycemia and glycosuria Favorable response to dietotherapy and insulin (p 1251)
Nutritional Edema	History of restricted protein diet, chronic infection, anemia malignancy or protracted diarrhea Slight to moderate hypoproteinemia Normal urine No elevation of blood cholesterol Infuse plasma or blood
Backward Failure	Normal blood chemistry and only mild to moderate albuminuria Favorable responses to digitalis diuretics and reduced fluid intake
Acute Nephritis	Earliest involvement of face Oliguria or anuria, albuminuria, hematuria and cylindruria (p 3683) Rising gradient of blood pressure (p 3486)
Hypertensive Toxemia of Pregnancy	Enlargement of uterus Rising gradient of blood pressure Albuminuria and hypoproteinemia (p 2639)
Capillary Toxicoses	Due to arsenic uranium radium lead, iodides, coal tar dyes spider venom, and snake venom. Get history
Burns	Of extensive areas with hypoproteinemia (p 706)
Menstrual Edema	Usually just before expected period. Retention of water and sodium chloride with gain in weight. Favorable response to ammonium salts and androgen (p 2401)
Desoxycorticosterone Edema	From excessive dosage in patients with Addison s disease (p 1277)
Thyroid Insufficiency	Non pitting myxedema Low BMR. Therapeutic response to thyroid extract (p 1189)
Beriberi	Thiamine chloride deficiency in wet stage Therapeutic test with Vitamin B (p 622)
Filariasis	Infection with Wuchereria bancrofti Lymph stasis with demonstration of microfilaria in blood (p 3324)

spaces by delaying renal excretion Derangements of antidiuretic factor result in diabetes insipidus

Certain hormones of the *adrenal cortex* (desoxycorticosterone) affect the electrolyte composition of body fluids by regulating the renal excretion of sodium and potassium This in turn may increase plasma volume favoring transudation It may be that adrenal cortex maintains the normal permeability of capillaries Many of the effects of the adrenal cortical hormones have been observed after the administration of *progesterone* This may be due to chemical similarity and may not be of physiologic significance

Thyroid hormone functions in the physiological interchange of fluid between tissues and capillary blood It accelerates the elimination of water and electrolytes by the kidney and increases blood volume In its absence there is a retention of water salt and protein in the tissue spaces productive of myxedema

Central Nervous Influences—The central nervous system exerts an important regulatory influence on water movement in the body This influence is mediated through effects on capillary endothelium changes in endocrine activity and other factors as yet undetermined

Certain hypothalamic centers the supra-optic nucleus controlling the posterior pituitary gland the heat regulating center and the center regulating the amount and distribution of adipose tissue may determine extensive alterations in the distribution of water in the body There may be a hypothalamic center directly controlling water metabolism

Hepatic Factors—As one of its many metabolic functions the liver may influence body hydration The existence of a hepatic diuretic hormone has been suggested The liver is the principal source of plasma proteins Through its control over the supply of these colloids it maintains the osmotic pressure of plasma The liver indirectly affects the volume of body fluids by regulating the destruction of steroid hormones Failure of this function favors their accumulation in the body and water retention

The clinical phenomena involving disturbances of the body fluid include dehydration (*anhydremia desiccation*) hyperhydration ("bulk reaction" water intoxication or *hyperhydremia*) decrease of plasma volume and increase of tissue fluid (*edema*)

DEHYDRATION
(*Anhydremia Desiccation*)

The state of dehydration prevails when all body fluids become impoverished It results from a negative water balance which may be caused by excessive fluid loss inadequate water intake or reduction in the quotas of sodium potassium carbonic acid and chloride

Excessive loss of fluid may be due to protracted vomiting intractable diarrhea excessive perspiration massive hemorrhage polyuria or profuse drainage from a fistula Fluid intake is inadequate in starvation depressions coma and unconsciousness

Clinical Manifestations—Dehydration produces rapid loss of body weight hemoconcentration a disturbance in the acid base balance toward the acid side a rise in blood catabolites manifest by azotemia and elevation of body temperature The skin appears dry wrinkled and loose the eyeballs feel soft and in infants the fontanelle is depressed

Differential Diagnosis—Recognition of the cause of dehydration requires only an investigation of the history

Treatment—In his treatment of dehydration the practitioner strives to eliminate fluid loss restore the normal content of water and correct the electrolyte pattern For the administration of water and electrolytes the oral route is used when possible Warm fluids are preferred The use of broth permits the addition of salt and tea may be sweetened with *sugar* Occasionally cold drinks are more tempting and carbonated beverages

of the blood the excretion of carbon dioxide by the lungs the renal excretion of excessive fixed acid or base and the steady flow of acid metabolites from cell to extracellular fluid The bicarbonate ion occupies a most important position with respect to acid base equilibrium Its concentration in plasma at any given time is a measure of the amount of residual

DIFFERENTIAL DIAGNOSIS OF

Decreased Basal Metabolic Rate

This condition is most frequently encountered in patients who do not have the clinical manifestations of classical myxedema Some of them are obese others lean. It has been our unconfirmed hypothesis that the overweight patient with a low metabolic rate represented a preclinical state of hypothyroidism, that the underweight individual with lowered basal metabolic rate constituted a forme fruste of a pituitary cachexia In any event the administration of thyroid extract under either of these circumstances may prove a therapeutic boon The obese patient will be assisted in weight reduction and, paradoxically the underweight person may develop so marked a sense of well being with accompanying bulimia that weight gain is registered Parenthetically the lean female who suffers concurrently from oligomenorrhea and sterility occasionally reports freer menstrual flow and she may even conceive

CAUSE	DIAGNOSTIC FEATURES
Starvation	History of under nutrition.
Anorexia Nervosa	History of undernutrition in psychopathic personality (p 1768)
Nephrosis	Generalized anasarca hypoproteinemia hypercholesterinemia, massive albuminuria doubly refractile lipoid substances in urinary sediment and reversal of serum albumin globulin ratio Refractory to thyroid extract. Diuresis with high protein diet (p 2389)
Anterior Pituitary Deficiency	Particularly in the pituitary cachexias (Simmonds disease) with leanness and asthenia (p 1169) Also in adiposogenital syndrome (Frohlich) with obesity and hypogonadism (p 1166)
Adrenal Cortical Deficiency	Addison's disease with hypotension, pigmentation and asthenia Therapeutic response *to sodium and desoxycorticosterone* (p. 1271)
Congenital Universal Asthenia	Glenard's syndrome with gastrovisceroptosis leanness, and weakness (p 1808)
Hypothyroidism	In cretinism and myxedema (p 1191) Therapeutic response to thyroid extract
Hypertrophic Osteo-Arthrosis	Skeletal disturbances of middle aged with obesity narrowing of joint spaces, thickening of articular surfaces and spur formation (p 2855)

base *after all* acids stronger than carbonic acid have been neutralized Alkali reserve therefore is a measure of the amount of base that is available for the neutralization of fixed acid and it is measured by the carbon dioxide content of plasma or serum Variations of alkali reserve indicate alterations in hydrogen ion concentration and their determinations are

monary edema and if the infusion is permitted to continue, cardiac failure may be produced

Treatment—The treatment of hyperhydremia involves discontinuance of the administration of fluids and reduction of the volume of circulating fluid by phlebotomy (p 852), if necessary

Diminution in Plasma Volume

Diminution in plasma volume occurs most strikingly in shock In this circumstance, due to increase in capillary permeability plasma exudes into the tissues and the circulating blood is concentrated as detected by the hematocrit

The condition of shock is described elsewhere (p 928) It is sufficient to note here that rational treatment consists of infusion of plasma or sodium r lactate rather than the injection of whole blood

Edema

Edema is the term applied to the presence of an excess of fluid in the tissues and/or serous cavities of the body Edema may be local or general in distribution depending upon the nature of the disturbance in the interchange of body fluid between vascular bed and tissue spaces

Clinically edema is manifest by local and generalized swelling (*anasarca*) gain of body weight and the presence of large amounts of free fluid in the body cavities (*ascites* or *hydrothorax*)

Pathogenesis of Generalized Edema—Edema results from those disturbances in the normal mechanisms of fluid equilibrium which lead to the accumulation of fluid in the tissue spaces The following principal causes of edema are recognized (*1*) *Reduction of osmotic pressure* of plasma colloids (*2*) *increase in hydrostatic pressure of capillary blood* (*3*) *increase in permeability of capillaries* (*4*) *retention of edema forming substances* (*hydropigenic*) such as water and sodium chloride (*5*) *lymphatic obstruction* Although one causative factor may predominate several different factors may be active in each instance

Edema Resulting from Decrease in Plasma Osmotic Pressure

Edema is encountered in a variety of conditions marked by hypoproteinemia Diminution in blood protein causes increased filtration of plasma through the capillary endothelium due to diminished colloidal osmotic pressure of plasma As a result, an excess of fluid and sodium chloride collects in the interstitial spaces Hypoproteinemia may be due to excessive proteinuria or diminished formation of plasma protein

Nephrotic Syndrome Due to Excessive Proteinuria—*Hypoproteinemia* and edema may follow prolonged loss of protein in the urine (*albuminuria*) This condition prevails in chronic nephrosis the nephrotic stage of chronic glomerulonephritis amyloid disease and diabetic nephrosis

Lipoid Nephrosis—Edema in chronic or lipoid nephrosis is due to the marked albuminuria which lowers the protein concentration of serum below 5 gm and the albumin content below 2.5 gm per cent The edema in this disease is peculiarly soft very extensive and pits easily on pressure The distribution of the fluid is influenced by gravity being most extensive over the lower parts of the body The peritoneal cavity vulva

DIFFERENTIAL DIAGNOSIS OF

Acidosis

During acidosis the body strains every resource to rid itself of excess acid. Respiration is increased to augment the elimination of carbonic acid. The urine becomes intensely acid with the pH falling to 4 6 Urinary formation of ammonia is increased, and there is usually a fall in the amount of base in the body and a corresponding fall in the volume of extracellular fluid until the patient shows evidences of dehydration. Aside from the disturbed electrolyte structure retention of fixed acid produces effects which vary with the mechanism by which the acidosis is produced.

CAUSE	DIAGNOSTIC FEATURES
Starvation and Dehydration	Excessive catabolism of fats leads to overproduction of short-chain fatty acids. Note acetonuria (p 3680)
Dietetic	*High fat low carbohydrate diets are ketogenic* Prescribed in urinary tract infections epilepsy and lead poisoning Note acetonuria (p 3680)
Pharmacodynamic	Ingestion of ammonium chloride or nitrate causes conversion of ammonium radical to urea and frees the acid radical which combines with base at the expense of bicarbonate *Saline acidosis used therapeutically to pro*duce diuresis in edema, to enhance the action of the mercurial diuretics, for urine acidification, in the treatment of epilepsy tetany lead poisoning and alkalosis
Diabetes Mellitus	Defective carbohydrate metabolism produces excessive catabolism of fat and overproduction of beta hydroxybutyric and aceto-acetic acid Alkali reserve is lowered and ketone bodies are excreted.
Other Endocrinopathies	*Follows experimental hypophysectomy and* pancreatectomy
Uremia	Impaired renal function leads to retention of fixed acid normally excreted in urine Alkali reserve is reduced and tendency to acidosis is aggravated by diminished ability of the damaged kidney to form ammonia Phosphate *retention leads to compensatory hyperpara*thyroidism and varying degrees of skeletal decalcification (renal rickets)
von Gierke s Disease	Defective hepatic glucogenesis and abnormal glycogen deposition results in increased catabolism of fats and resultant ketosis
General Anesthesia	Inhalations of ether chloroform, ethylene and nitrous oxide cause depletion of alkali reserve Cellular activity is depressed in response to anoxemia. Carbohydrate combustion is defective favoring the accumulation of large amounts of lactic acid and increased production of ketone bodies.
Toxic	Administration of sulfonamides and salicylates may result in mild decreases in alkaline reserve Either drug should be prescribed with equivalent doses of sodium bicarbonate.

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Blood calcium levels are dependent also upon adequate absorption of bone-forming minerals from the gastro intestinal tract This absorptive mechanism is influenced by vitamin D which facilitates the entry of diet ary calcium and phosphorus in the body Changes in serum protein are also accompanied by corresponding changes in calcium and there is an inverse relationship between the levels of calcium and inorganic phosphate in the serum

DIFFERENTIAL DIAGNOSIS OF

Hypercalcemia

Elevation of serum calcium indicates disturbances in the physiologic mechanisms which regulate the metabolism of calcium and phosphorus. High calcium figures are commonly associated with low readings for inorganic phosphate and increased excretion of both met abolites by the kidneys. Hypercalcemia tends to produce nausea and vomiting and favors the occurrence of renal insufficiency

CAUSE	DIAGNOSTIC FEATURES
Physiologic Hyperparathyroidism of Preg nancy	In last trimester the parathyroids hypertrophy and increase their activity for mobilization of maternal reserves of lime salts in order to assure the growth of the fetal skeleton Pre vent and treat by accessory calcium feedings
Primary Hyperparathyroidism	Due to parathyroid adenoma or profuse hyper plasia of all glandular structures (p 1226) Consider surgery
Renal Hyperparathyroidism	Protracted renal insufficiency produces para thyroid hyperplasia and hyperfunction, prob ably due to retention of inorganic phosphate
Hyperparathyroidism of Cushing Syndrome	Hypercalcemia accompanies basophilic aden omas of the anterior pituitary gland. This condition does not prevail with neoplasms of the adrenal cortex producing a similar syn drome
Pharmacodynamic	Large doses of potent parathyroid extract may produce an alarming hypercalcemia, attended by nausea vomiting diarrhea and collapse
Increased Bone Destruction	From increased liberation of lime in metastatic malignancy multiple myeloma leukemic in filtrations and polycythemia vera. Get hemo-gram and smear from bone marrow (p. 1043)
Sterol Hypercalcemia	Due to overdosage with vitamin D and dihy drotachysterol.

TETANY

Tetany is the state of increased neuromuscular irritability usually due to diminution in the concentration of ionized calcium in extracellular fluids

Latent Tetany —The presence of latent tetany is attested only by char acteristic responses to mechanical and electrical stimuli The facial phe nomenon of *Chvostek* is obtained by tapping the trunk of the facial nerve

elimination of the dye in all conditions in which there is marked albuminuria The presence of a chronic tuberculous lesion or some other form of suppuration favors the diagnosis of amyloid nephrosis as does the finding of hepatomegaly or splenomegaly due to amyloid infiltration of these organs Amyloid deposits in the kidney leading to the nephrotic syndrome *may occur without any other evidence of amyloidosis elsewhere* in the body

Diabetic Nephrosis—In elderly diabetics, edema associated with albuminuria and hypoproteinemia is not uncommonly encountered The edema is usually not as massive as in the previous examples of the syndrome Urinary and blood chemical findings are similar to those in chronic nephrosis but in addition there is a hyperglycemia with glycosuria

Treatment—The treatment of edema resulting from hypoproteinemia is concerned with the correction of the fundamental metabolic disturbances in the diabetic whose sugar metabolism first must be regulated The basic lesions in nephrosis nephritis and amyloiditis unfortunately cannot be attacked

Symptomatic treatment may be eminently satisfactory by the use of a high protein low fat diet (p 674) Repeated transfusions of citrated blood are useful most particularly with accompanying anemia The lowered basal metabolic rate is corrected by the administration of large doses of thyroid extract or intravenous injections of crystalized thyroxin

Diuretics (p 2257) are employed as temporary expedients The urine is rendered highly acid by ammonium salts (p 2259) after which a mercurial is given orally or intramuscularly (p 2261) The presence of albuminuria need not deter the practitioner from the use of the heavy metal so long as there is no significant hematuria

EDEMA RESULTING FROM DIMINISHED FORMATION OF PLASMA PROTEIN
(*Nutritional Edema*)

The formation of plasma protein is dependent on an adequate dietary intake of protein containing essential amino acids, unimpaired absorption of protein split products from the gastro intestinal tract and normal hepatic utilization of the precursors of plasma protein

The clinical causes of nutritional edema are tabulated below

Restricted Low Protein Diet
- Famine
- Disturbances of digestive tract associated with dysphagia anorexia or vomiting
- Avitaminosis (beri beri and pellagra) Hookworm disease

Excessive Protein Catabolism
- Chronic infection (tuberculosis brucellosis)
- Malignancy

Diminished Protein Absorption
- Chronic dysentery and ulcerative colitis
- Celiac disease
- Intestinal tuberculosis Hookworm disease
- Disturbances of digestive tract associated with diarrhea

inverted into palm and the fingers flexed at the metacarpophalangeal joints are bent over the thumb The wrist is acutely flexed and there is ulnar deviation of the hand The feet are in plantar flexion usually in a position of equinovarus The proximal phalanges of the toes are flexed the middle and distal rows extended the dorsum of the foot is prominent and the plantar surface is strongly arched Motion at the elbows shoulders hips and knee is relatively free although occasionally there may be stiffness and pain in the muscles controlling these joints Non pitting edema of the dorsal surfaces of the hands and feet may develop in carpopedal spasms of long duration

The muscles of the face and trunk also may be involved The face may appear rigid and stiff with the corners of the mouth drawn downward (carp mouth) and the forehead transversely wrinkled The entire body may be held rigid and the posture be that of opisthotonos simulating meningitis Strabismus nystagmus and pupillary inequality may occur

Spasm of the glottis (laryngospasm or laryngismus) is a frequent sign of tetany in infants The laryngeal muscles contract with such intensity that inspiration is partially or completely obstructed With partial obstruction there is a characteristic crowing sound with each inspiration resembling the whoop of pertussis The spasm may be mild and infrequent or it may occur as a series of attacks resulting in intense dyspnea cyanosis coma and death Laryngospasm is precipitated by slight reflex irritation such as emotional upsets cold draughts or sudden fear

Spasm of the diaphragm may produce inspiratory dyspnea with extreme cyanosis Rarely these may be expiratory dyspnea Laryngospasm is most common in children from 6 to 15 months of age but attacks may occur in adults

Generalized convulsions are common symptoms of tetany in infants They are nearly always bilateral and differ in no way from convulsions from other causes (p 1519) They may be precipitated by the slightest stimulus such as a loud noise or the application of cold to skin or they may come on spontaneously The number of attacks varies from an occasional episode to more than 80 a day Death rarely occurs after a rapid succession of attacks

In addition to the cardinal symptoms of tetany a great variety of other symptoms and signs also are encountered *Spasms* have been noted in the *ciliary muscle* and the muscles of *iris esophagus stomach intestines urinary bladder bronchi* and *heart* Intractable vomiting and urinary retention may be present Bronchotetany may produce marked dyspnea tachypnea cyanosis fever atelectasis emphysema pneumonitis and "asthmatic attacks

In infants tetany may produce *cardiac spasm* with sudden death Cardiac spasm bears no relation to the severity of the tetany and has been encountered with few other symptoms or with repeated convulsions Tachycardia and arrhythmias are not uncommon manifestations of mild and latent tetany Other circulatory abnormalities include *angiospasms* of fingers and toes and *dermographism*

Although tetany is usually an acute condition it may become chronic in a latent or active form *Chronic tetany* leads to a variety of trophic changes involving ectodermal structures Alopecia brittleness and groov

the portal veins the vessels of the extremities and in arteriovenous aneurysms

Obstruction of the Superior Vena Cava—Gradual encroachment on the superior vena cava usually by a mediastinal tumor causes edema and anosis of the upper part of the body the face and arms The retinal ins may show intense engorgement and hemorrhages Involvement of one nominate or subclavian vein causes edema and cyanosis of the upper tremity drained by the affected vein In cases of superior vena caval struction the venous pressure in both arms is usually sharply elevated iere is a well marked venous pattern over the chest and abdomen caused the formation of a collateral venous circulation between internal mam ary and inferior epigastric vessels This may be dramatically demon ated by means of infrared photography

Obstruction of the Inferior Vena Cava—Obstruction of the inferior na cava usually by carcinomatous involvement or compression produces ema of the lower extremities and lower abdominal wall There is eleva n in femoral venous pressure and formation of a venous pattern over e lower abdomen due to the collateral circulation

Portal Obstruction (Portal Hypertension)—Impairment of the portal culation causes back pressure in the portal circuit and the formation of cites The commonest cause of this condition is cirrhosis of the liver here there is gradual obliteration by fibrous tissue of the fine portal nules Other causes include pressure by tumor masses on the main portal ibutaries or thrombosis of the portal vein

The clinical phenomena depend upon the extent and rapidity of the struction In cirrhosis of the liver the process of venous occlusion is ow and ascites appears in only 50 per cent of fatal cases usually as a sult of failure of the collateral circulation In some cases it is precipitated an acute toxic hepatitis which causes severe parenchymal injury and llapse of the portal intrahepatic tributaries Perihepatitis frequently adds the chronicity of the ascites Ascitic fluid is rich in albumin and repeated racentesis constitutes an important source of protein loss which may vor the development of hypoproteinemia Other factors increasing the lematous tendency are intrinsic disease of the liver impaired absorption protein from the edematous intestinal tract and pressure of the mass of scitic fluid on the venous channels impeding venous return

Thrombosis of the portal vein causes rapidly appearing ascites and ute enlargement of the spleen There may be associated thrombocyto enia and a hemorrhagic tendency An old partial portal vein thrombosis believed to be the cause of some cases of Banti s disease with cirrhosis ad splenic fibrosis

Obstruction of Veins of the Extremities—Obstruction is an important ause of edema in the lower extremities During pregnancy the enlarging terus compresses the iliac veins and favors the development of edema and aricose veins In many cases a superimposed thrombophlebitis adds to he stasis A large uterine or ovarian tumor may cause a leg edema by iac compression Not uncommonly a large splenic tumor as seen in leu emia Gaucher s disease or polycythemia vera may increase intra abdom ial pressure and impede the return of venous blood from the legs

Thrombosis is a common cause of saphenous obstruction This is fa

treatment of tetany is disappointing It relieves the acute attacks but it is of limited value in chronic cases Patients become refractory and may develop untoward reactions The hormone accomplishes little that cannot be obtained by simpler methods of therapy

Parathyroid Transplantation—In a few cases of hypoparathyroidism successful grafts of human parathyroid tissue have produced remarkable improvement The graft is usually obtained during thyroidectomy or the resection of parathyroid tissue for hyperparathyroidism It is inserted into the rectus abdominis muscle of the recipient

Activated Sterols—Irradiation of ergosterol leads to the formation of a number of sterols without antirachitic properties but capable of producing a marked rise in serum calcium The action is nonspecific and is possessed by vitamin D vitamin D_3 tachysterol dihydrotachysterol and other closely related compounds

DIFFERENTIAL DIAGNOSIS OF

Hyperphosphatemia

In hyperphosphatemia, the serum phosphate level may rise beyond 7 mg per 100 cc

CAUSE	DIAGNOSTIC FEATURES
Hypervitaminosis D	Excessive doses of vitamin D particularly as employed in the treatment of the chronic *arthropathies and prolonged exposure to* ultraviolet, may produce pronounced hyperphosphatemia
Hypoparathyroidism	With reciprocal diminution in serum calcium, leading to parathyroid tetany
Renal Insufficiency	In chronic glomerulonephritis with fixation of specific gravity of urine and azotemia Retention beyond 8 mg per 100 cc of serious prognostic importance
Healing of Fractures	Values up to 7 mg per 100 cc

Vitamin D_2 (calciferol) *viosterol* (50 per cent calciferol lumesterol and tachysterol) and *dihydrotachysterol* (A T 10) have proved effective in raising the blood calcium level in hypoparathyroidism The mode of action is apparently on the skeleton although there is also some effect on the absorption of calcium from the intestine and increased renal excretion of inorganic phosphate which may act to mobilize skeletal calcium

Treatment of hypoparathyroidism is carried out with large initial doses of these sterols followed by smaller maintenance doses It is usual to give 3 to 10 cc (3 75 to 12 5 mg) of dihydrotachysterol in oil (*Hytakerol*) 10 to 40 mg of calciferol or 400 000 to 1 000 000 units of vitamin D for the first few days until the blood calcium level rises to normal When tetany is relieved the maintenance dose is arrived at by trial and depends on the severity of the hypoparathyroidism and the amount of calcium in the diet Usually 3 to 5 cc of dihydrotachysterol are sufficient and the corresponding dose of calciferol is 3 to 5 mg

efficiency and accentuates cardiac difficulty by interfering with the descent of the diaphragm Failure of the right heart may occur in the presence of a competent left ventricle In such cases there will be no pulmonary edema and little respiratory difficulty

As a rule cardiac failure involves *both ventricles* and the resultant picture is a composite Mechanical factors determine the localization of edema fluid in many instances of cardiac failure The pressure of the dilated auricles on the azygos vein favors the development of right hydro thorax The pressure of ascitic fluid on the iliac veins may further increase the stasis of blood in the lower extremities Marked dilatation of the left ventricle with the bulging of the intraventricular septum to the right narrows the lumen of the right ventricle and increases systemic stasis (Bernheim s syndrome)

In addition to the primary cardiac defect chronic cardiacs are prone to the development of hypoproteinemia which aggravates the tendency to edema The absorption of protein from the intestinal tract is defective due to the edema of the intestinal wall There is probably a reduced rate of production of plasma protein due to anoxemia and edema of the liver

In cardiac edema the protein content of the edema fluid is variable but is usually about 0 5 per cent A detailed consideration of the clinical study of cardiovascular dynamics that enter into the production of edema is found with the material on *Backward Failure* (p 942)

Extensive edema produces a variety of deleterious effects on patients with cardiac disease The edema fluid impairs the functioning of vital or gans (liver lungs intestinal tract and heart) Large accumulations of fluid hinder the circulation in peripheral areas and increase local tissue anoxemia The presence of extensive edema of the subcutaneous tissues tends to impair the elimination of heat and interferes with insensible per spiration This in turn increases the basal metabolic rate and the work of the heart

In cases of adhesive and constrictive pericarditis edema may be chiefly mechanical due to stasis produced by adhesions interfering with the in flow of blood to the heart There may be persistent elevation of venous pressure and chronic edema refractory to therapy due to the presence of bands deforming the inferior and superior venae cavae and the auricles

Treatment—The treatment of heart failure is considered elsewhere In addition to measures directed at correction of the circulatory derange ments the patient is given a diet that is low in fluid (p 664) Serous collections are mechanically evacuated and digitalis and diuretics find their greatest fields for employment (p 2257) With demonstrable hypopro teinemia a high protein diet is considered (p 674)

EDEMA DUE TO INCREASED CAPILLARY PERMEABILITY

Increase in permeability of capillary endothelium disrupts the selec tive communication between vascular and extravascular fluid compart ments Plasma colloids gain free access to tissue spaces and add to the tenacity with which *the interstitial fluid is held In most instances* there is widespread capillary engorgement and increase in the circulation of the affected area These factors contribute to the tendency to edema forma tion In view of the many influences that are capable [illegible]

In using these compounds *overdosage* is prevented by using the calcium content of the urine as a guide For this purpose, the simple Sulkowitch reaction is helpful (p 1229) Hypocalcemia and hypercalcemia are reflected by the changes in the amount of calcium precipitated by the buffered oxalate solution There is no evidence that dihydrotachysterol possesses any advantage over equivalent doses of calciferol or viosterol The patient with hypoparathyroidism learns to regulate his own dosage by the depth of the urine calcium cloud in much the same manner that a diabetic adjusts his insulin to the glycosuria

DIFFERENTIAL DIAGNOSIS OF *Hyponatremia*

In excessive hyponatremia the serum sodium may fall below 100 mg per liter Under these circumstances, the patient may suffer serious symptoms as the result of severe forward failure (p 920)

CAUSE	DIAGNOSTIC FEATURES
Loss of Fluid	In prolonged vomiting and pyloric obstruction, protracted diarrhea long standing biliary or intestinal fistulas profuse perspiration followed by the ingestion of pure water and excessive diuresis particularly with the mercurials Treat by salt ingestion or injection.
Diabetes Mellitus	In severe acidosis and loss of fixed base in combination with ketone bodies Use saline infusions
Renal Insufficiency	Inadequate reabsorption of sodium by the kidneys and excessive excretion in the urine Tendency augmented by diet containing limited quantities of salt
Miners and Stokers Cramps	In heavy industries associated with profuse sweating May result from the drinking of excessive quantities of water containing little or no salts Provide salt tablets
Adrenal Cortical Deficiency	Particularly low figures in acute crises which may be prevented and treated by the ingestion or administration of sodium chloride (p 1276)
Lobar Pneumonia	Due to increased storage of sodium in tissues or retention in exudate Similar changes may occur in erysipelas typhoid fever and pulmonary tuberculosis.

DISTURBANCES OF PHOSPHORUS METABOLISM

Disturbances of phosphorus metabolism are infrequently of clinical importance Determinations of serum phosphates are rarely made despite the fact that they are of incalculable value in interpreting abnormalities in the metabolism of calcium The normal value is 3 to 4.5 mg per 100 cc in adults and 4 to 6 mg in children

DISTURBANCES OF SERUM PHOSPHATASE

Phosphatase is the enzyme that liberates organic phosphate through the hydrolysis of esters of monophosphoric acid It is present in almost

obstruction as in the larynx Symptomatic relief is best afforded by cold or iced wet dressings

Acute Nephritis —In acute nephritis, there is widespread injury to capillaries especially those in the kidney and generalized increase in capillary permeability The cause of this injury is unknown but it may be the result of an allergic state incident to the process of immunization to primary infection The capillary injury may be direct or it may result from arterial spasm producing capillary anoxemia

Edema is commonly but not invariably present in an acute nephritis Its appearance may be gradual or sudden Usually it affects the face especially the loose cellular tissue of the eyelids producing the nephritic facies Scrotum vulva peritoneum and pleural or pericardial cavities may be involved and generalized anasarca may be present Acute cerebral episodes may result from cerebral vascular changes spasm or edema The pia may be edematous and cerebrospinal fluid pressure may be increased

The ingestion of salt by the patient with acute nephritis may produce acute cerebral symptoms such as convulsions amaurosis hemiplegia and coma Sudden myocardial insufficiency may occur in the course of acute nephritis and contribute to the edema

Pregnancy Toxemias —Edema encountered during pregnancy may originate in several ways Increased intra abdominal pressure from pressure of the enlarging uterus on the iliac veins favors edema formation in the extremities Acute angiospastic phenomena produce edema as an early and important symptom of grave importance A primary retention of water and sodium chloride may result from endocrine imbalance Massive albuminuria may produce hypoproteinemia See *Hypertensive Toxemia of Pregnancy* (p 2639)

Rheumatic Fever —Edema is a prominent symptom of the rheumatic state The basic tissue injury is obscure but it may be the manifestation of an antigen antibody reaction Capillaries are particularly vulnerable with the result that hemorrhagic manifestations and collections of edema in affected areas are commonly noted The large joints may contain appreciable amounts of fluid massive pericardial effusions produce cardiac embarrassment pleural effusions and intraperitoneal edematous lesions may be encountered and urticarial wheals and a variety of erythematous and edematous skin lesions are seen (p 190) Generalized edema of cardiac origin occurs if there is complicating myocardial failure due to involvement of heart muscle and endocardium by the rheumatic process Rheumatic edema subsides almost specifically with salicylate therapy (p 3832)

Chemical Capillary Toxicoses —Chemical poisons may cause widespread capillary injury and increase in permeability by a direct action on capillary endothelium The offenders include arsenic uranium radium, lead and other general protoplasmic poisons In susceptible individuals, exposure to sunlight leads to the formation of hematoporphyrin and the production of edema Iodides and certain coal tar dyes especially paraphenylenediamine cause increase in capillary permeability and extensive edema Bee spider and snake venoms are capillary poisons which on entrance to the body produce widespread edema Laryngeal edema may cause serious respiratory difficulty in persons bitten by insects and snakes

Infestation with *Trichina spiralis* (p 539) produces extensive perior

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Phosphatase is the enzyme that liberates organic phosphate through the hydrolysis of esters of monophosphoric acid It is present in almost

tive heart failure The myocardial strain may be precipitated by sudden increase in blood volume by elevation of blood pressure and by electrolyte changes that affect myocardial efficiency (extreme lowering of plasma potassium and replacement of intracellular potassium by sodium)

Posterior Pituitary Edema —The administration of large quantities of water to patients receiving pituitary antidiuretic factor produces water retention which may lead to water intoxication Edema is one of the early evidences of excessive hydration The urine is scant and often contains albumin and large amounts of sodium chloride Muscle tremors and headache are common Convulsions may result from cerebral edema Excessive hemodilution and intravascular hemolysis have been produced experimentally by injections of pituitary antidiuretic factor in animals and antidiuretic factor may be demonstrated in the urine of patients with various types of edema

Overactivity of posterior lobe pituitary during the latter part of pregnancy has been suggested as an etiologic factor in pregnancy toxemia a condition in which edema is common Study of blood and urine of toxemic patients reveals the presence of an antidiuretic factor believed by some to be of pituitary origin

Myxedema —Thyroid hypofunction produces retention of salt water and protein in the tissue spaces The skin becomes dry rough and swollen but inelastic not pitting on pressure It is pale with a slightly yellow tint Originally it was thought that these changes resulted from the overproduction of mucin which flooded the subcutaneous tissue spaces (myxedema) Recent observations confirm the existence of extravascular and extracellular increase in mucoprotein in hypothyroidism In addition to retained protein deposit protein and appreciable quantities of water and sodium chloride are stored The administration of thyroid causes increased elimination of nitrogen in the urine and an appreciable diuresis

ABNORMALITIES OF OXYGEN CONSUMPTION

The rate of oxygen consumption is estimated by measuring the basal metabolic rate under standard conditions (p 3738) Corrections are made for age sex body surface as calculated from the height and weight of the subject barometric pressure and the temperature of the machine

The basal metabolic rate may be within normal limits or above or below normal Since normal figures are based on *averages* (p 3739) the clinician must not be rigid in his interpretation of the data presented by the laboratory Many patients have a basal metabolic rate as low as minus 10 or minus 15 per cent without symptoms referable to the reading Less often a report in the zone of plus 5 to plus 15 per cent is unassociated with clinical abnormalities The determination of the basal metabolic rate is of importance only in the light of the attendant clinical phenomena

Elevation of the basal metabolic rate must be differentiated from increased oxygen consumption The latter is due to *technical errors* such as making the determination after the patient has ingested food in association with pyrexia with dyspnea due to saturation of the soda lime in the apparatus failure of the patient to relax so that the record reveals an uneven trace with bradypnea, tachypnea, air swallowing and ratory

Variations in serum potassium though rare are poorly tolerated In creases lead to nausea vomiting and circulatory collapse whilst decreases produce muscle weakness and paralysis

DIFFERENTIAL DIAGNOSIS OF

Hyperpotassemia

A significant increase in the concentration of serum potassium may lead to levels of 7 to 8 milliequivalents with attendant gastro-intestinal disturbances and circulatory failure

CAUSE	DIAGNOSTIC FEATURES
Adrenal Cortical Deficiency	In Addison s disease high levels are present in the crisis and may be responsible for many of the clinical symptoms The administration of potassium may produce an acute crisis within a few hours (p 1271)
Renal Insufficiency	*Potassium retention may be responsible for* many of the gastro-intestinal symptoms of uremia The use of potassium salts for diuresis is contra indicated
Intestinal Obstruction	Retention of serum potassium in intestinal ob struction may produce toxic manifestations favoring the onset of forward failure (p 920)
Burns	Increased values may result from plasma loss and acute adrenal insufficiency (p 1268)

DIFFERENTIAL DIAGNOSIS OF

Hypopotassemia

Hypopotassemia is encountered even less frequently than retention of the element Its sig nificance lies in the fact that it may produce muscle weakness and paralysis

CAUSE	DIAGNOSTIC FEATURES
Adrenal Cortical Hyperfunction	With adrenal cortical tumors and increased *doses of desoxycorticosterone depressior of* potassium levels may produce asthenia and intermittent paralyses Administration of po tassium chloride prevents and relieves these conditions (p 1268)
Familial Periodic Paralysis	Low levels observed during attacks which are associated with marked increases in urinary excretion Administration of potassium salts prevents and relieves paralyses (p 600)

DISTURBANCES OF CHLORIDE METABOLISM

The chloride content of whole blood ranges from 450 to 500 mg per 100 cc the normal values of plasma are 570 to 620 mg per 100 cc Chlo ride is eliminated from the body chiefly in the urine to a lesser extent in the sweat and feces

irregularities leakage of oxygen around the mouthpiece or through tubing and similar difficulties

The basal metabolic rate is checked with the basal pulse rate Once a relationship is established the two findings vary proportionally Dispro portion between the two requires investigation i e bradycardia and an elevated basal rate or tachycardia and a normal rate

FEVER OF METABOLIC ORIGIN

In the discussion of fever (p 19) emphasis was placed upon eleva tions in temperature due to aseptic causation Some of these latter are metabolic disorders as undernoted

DIFFERENTIAL DIAGNOSIS OF *Fever of Metabolic Origin*

CAUSE	DIAGNOSTIC FEATURES
Starvation	History
Dehydration	Result of excessive vomiting diarrhea, loss of fluid through fistulas intestinal drainage or excessive sweating
Diabetic Coma	Glycosuria hyperglycemia acetonuria and acidosis (p 1251)
Uremia	Azotemia albuminuria and fixation of specific gravity (p 2276)
Thyrotoxicosis	In acute storm with marked restlessness or coma tachycardia elevation of BMR and ex cessive sweating Often follows operation or acute infection (p 1207)
Gout	Podagra or other evidences of arthritis Tophi particularly in ear and uricacidemia (p 2867)
Drug Fever	Primary and secondary fevers with toxi coderma in arsenotherapy in syphilis and with sulfonamide (p 94)
Anemia	Hemogram shows diminution in hemoglobin and red count (p 1055)
Leukemia	Characteristic hemogram showing alteration in white cells and either leukopenia or marked leukocytosis (p 1100)

DISTURBANCES OF HYDROGEN ION CONCENTRATION (pH)

Extracellular fluid is the immediate environment of the living cell The successful performance of vital processes by the cells requires an approxi mate constancy of temperature osmotic pressure and hydrogen ion con centration (pH) The electrolyte structure of extracellular fluids termed the chemical anatomy' determines the constancy of physiochemical rela tionships This mechanism is dependent greatly upon the hydrogen ion concentration which is maintained in extracellular fluids close to a pH of 7 4 and within the narrow limits of 6 8 to 7 8

The constancy of hydrogen ion concentration is accomplished by a number of integrated physiologic mechanisms These inclu buffers

have a high renal threshold and whose storage mechanisms for carbohydrate are defective Plasma yields higher sugar values than whole blood and arterial blood contains more than venous blood

Clinical Manifestations of Hypoglycemia —The clinical manifestations of hypoglycemia are chiefly in the realm of the nervous system since neurogenic tissue is dependent entirely on carbohydrate for energy require-

DIFFERENTIAL DIAGNOSIS OF

Hyperglycemia

Elevation of the level of blood sugar is observed most frequently in diabetes mellitus but hyperglycemias also may be associated with a variety of other abnormalities

CAUSE	DIAGNOSTIC FEATURES
Psychogenic	In association with fear and other emotional disturbances
Medullary	With piqure under experimental conditions and in association with increases in intracranial tension from trauma brain abscess or cerebral neoplasms.
Pharmacodynamic	Following injections of epinephrine and allied preparations
Toxic	With asphyxia, especially that associated with anesthetic poisoning from ether and chloroform (p 3926) From nicotinism and excessive smoking
Convulsive	*With convulsive disorders of whatever etiology* (p 1519)
Hyperthyroidism	In Graves disease (p 1197) with elevation of BMR and occasional transitory glycosuria
Hyperpituitarism	In early stages of gigantism, acromegaly and Cushing s syndrome (p 1153)
Adrenal Cortical Hypersecretion	With chromaffinomas often associated with virilism and hypertension (p 1268)
Hypoinsulinism	Most frequently in diabetes mellitus with polyuria, polydipsia and glycosuria (p 1246)
Acidosis	Due to increased glycogenolysis by the liver (p 721)

ments The repertory of disturbances produced by hypoglycemia is tabulated below

Nervous

- AUTONOMIC —Sweating pallor tachycardia hypertension salivation and lacrimation
- PSYCHIC —Anxiety confusion irritability catatonia hallucinations depression mania and delirium
- BULBOPONTINE —Disturbance of speech mask like facies diplopia nystagmus anisocoria or mydriasis
- CORTICOSPINAL —Jacksonian convulsion mono and hemiplegias areflexia unilateral or bilateral Babinski signs aphasia amnesia involuntary defecation and micturition and amaurosis

utilized to establish the presence of acidosis or alkalosis In acidosis alkali reserve is reduced and fixed acid is produced in excess or is retained in ordinately in the body In alkalosis alkali reserve is increased and there is an excess of fixed base over fixed acid in the extra cellular fluids Changes in hydrogen ion concentration therefore are tantamount to the states of acidosis or alkalosis

DISTURBANCES OF ALKALI RESERVE

The disturbances of alkali reserve include acidosis a state of decreased and alkalosis a state of increased carbon dioxide content of plasma or serum In acidosis the normal level of 55 to 60 volumes per cent may fall as low as 10 in alkalosis the reading may reach 120 volumes per cent.

DIFFERENTIAL DIAGNOSIS OF

Increased Basal Metabolic Rate

In the absence of fever elevation of the basal metabolic rate most strongly suggests hyper thyroidism

CAUSE	DIAGNOSTIC FEATURES
Fever	Rectal temperature in excess of 100°F
Leukemia	Abnormal leukocytes in smears obtained from peripheral blood or bone marrow (p 1100)
Polycythemia	Increase in erythrocytes beyond 7 000 000 per cu mm and hematocrit reading beyond 55 per cent (p. 1092)
Diabetes Insipidus	Marked polyuria and polydipsia responding to the pituitary antidiuretic factor (p 1180)
Backward Failure	Obvious circulatory disease edema, dyspnea and diminished vital capacity
Hyperthyroidism	Tachycardia goiter exophthalmos tremor and elevation of BMR. Therapeutic response to iodide (p 1213)
Hyperpituitarism	In early stages of giantism (p 1153) and acromegaly (p 1156)

DISTURBANCES IN CALCIUM METABOLISM

Normal serum contains from 9 to 11 mg of calcium per 100 cc Total calcium consists of a *diffusible* and almost completely ionized portion ranging from 4 5 to 5.5 mg and a *non diffusible portion* bound to serum protein amounting to 4.5 to 6 mg per 100 cc By means of a nomogram the concentrations of ionized and protein bound calcium may be derived from the figures for total calcium and total protein

Factors Influencing the Normal Concentration of Serum Calcium—The normal serum calcium level is maintained within narrow limits by the inter action of a number of physiologic mechanisms The most important of these is the degree of parathyroid function which regulates the excretion of phosphorus and the liberation and deposition of lime salts in the skeleton Increased parathyroid activity produces elevatio[illegible]

Paralytic Stage —Convulsions and paralyses
Coma
Death

Treatment of Hypoglycemia —The treatment of hypoglycemia involves an immediate injection of epinephrine and oral or intravenous administration of readily available sugar in the form of dextrose Diabetics receiving insulin should never travel without a piece of candy or a lump of

DIFFERENTIAL DIAGNOSIS OF

Hyperproteinemia

Hyperproteinemia is usually in essence a hyperglobulinemia with reversal of the albumin globulin ratio Only rarely is the condition the result of increases in plasma fibrinogen

CAUSE	DIAGNOSTIC FEATURES
Multiple Myeloma	Excessive globulin concentration with characteristic skeletal changes and Bence Jones proteinuria (p 1126)
Lymphopathia Venereum	Increase in globulin fraction with inversion of albumin globulin ratio and moderate increase in fibrinogen. Particularly marked in late phases with strictures of the rectum (p 471) Do Frei test (p 473)
Kala azar	Hyperglobulinemia with inversion of albumin globulin ratio in systemic leishmaniasis Detected by positive Napier aldehyde reaction of serum (p 534)
Schistosomiasis	Disturbances as in kala-azar Search urine *and stools for ova*
Dehydration	Due to hemoconcentration and increase in plasma globulin associated with burns diabetic acidosis intestinal obstruction and the crises of Addison s disease
Generalized Infections	Hyperglobulinemia in subacute bacterial endocarditis malaria tuberculous adenitis syphilis filariasis trypanosomiasis in addition to schistosomiasis and kala azar mentioned above
Blood Dyscrasias	Hyperglobulinemia in leukemia and lymphosarcoma (p 1100) Get hemogram marrow smears and biopsy

sugar and members of the household are instructed to have available an ampoule of 1 1000 epinephrine solution for immediate use if necessary

The non diabetic with hypoglycemia requires intensive investigation which may *necessitate exploratory laparotomy for the purpose of reveal*ing adenomas of the pancreas if the symptoms are sufficiently intense and incapacitating (p 1242)

DISTURBANCES OF PROTEIN METABOLISM

The plasma of the normal individual contains from 6 to 8 gm of total protein The ratio of albumin to globulin varies between 1 43 and 1 72

and depression of serum inorganic phosphorus, decreased parathyroid function is attended by a fall in calcium concentration and a rise in inorganic

DIFFERENTIAL DIAGNOSIS OF

Alkalosis

Alkalosis results when excessive amounts of acid are lost from the body without corresponding losses of base It also may be produced when alkali is supplied or formed in excess of the capacity of the body to neutralize or eliminate it.

CAUSE	DIAGNOSTIC FEATURES
Hyperventilation	Excessively deep and rapid respirations result in the elimination of abnormally large amounts of carbonic acid from pulmonary alveoli. A relative excess of alkali is found in extra cellular fluid and increased amounts of bicarbonate are excreted in the urine The urinary output of acid phosphate is decreased whilst the alkaline phosphates are eliminated in excess The formation of urinary ammonium salts and alkalosis is the resultant summation of the metabolic disorder Hyperventilation may be hysterical febrile encephalitic or the result of high external temperatures
Vomiting	Continued loss of hydrochloric acid from the stomach produces increased alkali reserve with hypochloremia and azotemia. Fixed base and carbonate are excreted in excess in the urine Similar changes are produced by frequent gastric lavage and continuous drainage in decompressive procedures. Treat by intravenous infusions of saline solution (p 3775)
Pharmacodynamic	Increased ingestion of large amounts of absorbable alkaline salts such as sodium bicarbonate produces alkalosis Plasma carbon dioxide is increased, blood chlorides are decreased, nonprotein nitrogen is elevated and renal function is depressed The metabolic disturbance may result from antacid given in the treatment of hyperacidity and peptic ulcer Correct by substitution of non absorbable alkali (p 1755)
Endocrinologic	An increase in serum carbon dioxide is encountered in patients with adrenal cortical tumors and basophilic adenomas of the anterior pituitary gland. Serum sodium is increased while chloride and potassium are decreased The metabolic disturbance may also result from injections of desoxycorticosterone (p 1277)
Roentgen Therapy	Increased alkali reserve results in patients receiving x ray and radium therapy Serum phosphate and chloride are decreased and pH is diminished.

phosphates The mechanism by which the hormone operates is apparently dependent upon changes in the bone and kidneys

compatible blood an increase in the sedimentation rate failure of clot retraction rapid coagulation and anti complementary Wassermann tests

Elevation of the Blood Nonprotein Nitrogen (Azotemia)—Increase in the nonprotein nitrogenous constituents of the blood is designated an azotemia The disturbance may be the result of increased catabolism or failure of the renal excretory mechanism *The discussions of azotemia and the differential diagnostic features are more properly placed in the section devoted to* Urinary Disturbances (p 2276)

DIFFERENTIAL DIAGNOSIS OF

Hyperuricemia

The normal blood uric acid level varies between 2 and 4 mg per 100 cc With increased levels the figures may rise as high as 10 or 12 mg

CAUSE	DIAGNOSTIC FEATURES
Renal Insufficiency	Retention of blood uric acid may precede azotemia
Gout	Acute attacks almost invariably associated with increases to 6 or 10 mg per 100 cc (p 2867)
Leukemia	Increased destruction of nucleoprotein elevates blood uric acid particularly in myelogenous variety Get hemogram (p 1100)
Multiple Myeloma	As in leukemia Note skeletal changes and presence of Bence Jones proteose in urine (p 1120) Get bone x rays
Pernicious Anemia	In remissions as result of general increase of nuclear metabolism throughout the body Study hemogram (p 1077)
Chronic Lead Poisoning	Presumably in association with renal insufficiency (p 7o2)
Eclampsia	As result of increased endogenous nucleoprotein metabolism (p 2638)
Intestinal Obstruction	Together with azotemia (p 2270)

DISTURBANCES OF URIC ACID METABOLISM

Abnormalities of uric acid metabolism are of chief clinical significance in gout (p 2867) *Hyperuricemia may occur in a variety of other conditions* under which circumstance an attack of gout may be precipitated Diminution in the blood uric acid so far as is known has no importance

DISTURBANCES OF LIPID METABOLISM

Lipid metabolism is best studied through the plasma cholesterol and cholesterol ester determinations The normal figures are subject to wide fluctuations and may vary between 130 and 170 mg per 100 cc of which approximately half is esterified At birth plasma cholesterol figures are as low as 50 mg per cent but an increase to adult levels occurs within a few

thereby producing momentary contraction of the facial muscles The peroneal sign is elicited similarly by striking the nerve as it winds around the lateral surface of the fibula A positive response consists of dorsiflexion and adduction of the foot *Trousseau s phenomenon* is manifested as the result of pressure on the blood vessels that serve the arm When the circulation is occluded with a blood pressure cuff a positive response is one in which the fingers and hands assume the obstetrical position The demon

DIFFERENTIAL DIAGNOSIS OF

Hypocalcemia

Hypocalcemia may be produced by a diet that is deficient in calcium phosphorus and vitamin D by hypoparathyroidism and by interference with the alimentary absorption of the lime salts and vitamin D These conditions decrease the concentration of ionized calcium and lead to the clinical condition of tetany next to be described (p 723) Diminution in the non-diffusible fraction of the calcium is observed in nephrosis and chronic nephritis with edema and, under these circumstances tetany does not occur

CAUSE	DIAGNOSTIC FEATURES
Dietary Deficiency	In association with rickets osteomalacia pregnancy and lactation. Observe therapeutic test with calcium and Vitamin D (p 620)
Hypoparathyroidism	In the newborn, following operation and as an idiopathic disturbance Administer calcium and Vitamin D
Alimentary	In intestinal disturbances such as celiac disease sprue pancreatic steatorrhea and inflammatory disturbances like ileocolitis Fats are not absorbed and form insoluble calcium salts preventing the absorption and assimilation of lime Fat soluble vitamin D is excreted, adding to the metabolic defect. Give calcium intramuscularly (p 3772)
Alkalosis	See p 722
Inactivation of Calcium	Through parenteral administrations of oxalate and citrate
Pharmacodynamic	Due to poisoning with lead, atropine strychnine and guanidine
Nephrosis	Decrease in non-diffusible fraction resulting from hypoproteinemia, without production of tetany Treat protein deficiency (p 674)
Chronic Nephritis with Edema	Same as nephrosis
Kala Azar	With decrease in the concentration of serum albumin, secondary to hyperglobulinemia

stration of *Erb s sign* requires the use of a galvanometer Neuromuscular responses are obtained with weaker stimuli than are required in normal individuals

Manifest Tetany —The most frequent symptoms of manifest tetany are carpopedal spasm laryngospasm and convulsions *Carpopedal spasms* may develop abruptly or they may be preceded by paresthesias in the extremities The upper extremities are usually affected first and with equal intensity The position of the hand is typical the fist is clenched with thumb

days There is apparently an inverse relationship between the blood content of cholesterol and protein as is discussed at greater length in the material devoted to the subject of hypoproteinemia (p 707)

DISTURBANCES OF THE LIPIDS OTHER THAN CHOLESTEROL

Though little is known of the lipids with the exception of cholesterol hyperlipemia may occur in a variety of disturbances that are imperfectly understood at the present time

ing of the finger nails hypoplasia of dental enamel and cataracts may be encountered In young adults the last are usually nuclear while in older patients they are apt to be cortical

Tetany also may result in hallucinations mental confusion apathy and stupor Usually, the mental picture clears with the alleviation of the metabolic effect

Treatment—The rational treatment of tetany necessitates thorough understanding of the physiologic mechanisms involved in its production As a rule acute episodes are relieved by parenteral administration of calcium salts but attacks recur unless the cause is removed or the chemical disturbance is counteracted by other means

The tetany of *lime salt and vitamin D deficiency* disappears with correction of the dietary inadequacy When intestinal absorption of these substances is compromised by local enteric disease or pancreatic insufficiency large doses of vitamin D and a high calcium low phophorus diet are beneficial in some cases but in others little can be accomplished *Alkalotic tetany* subsides with the correction of the underlying disturbance in acid base equilibrium but the tetany of nephritis is usually a preterminal symptom

The tetany of *hypoparathyroidism* is often a difficult problem because of its severity and chronicity It may require the administration of calcium a low phosphorus diet feedings of aluminum hydroxide substitution therapy with parathyroid extracts or transplants and elevation of the blood calcium level and decrease of inorganic phosphorus by activated sterols related to vitamin D (dihydrotachysterol)

Calcium Salts—Calcium salts may be given orally or parenterally For *oral* use the *chloride carbonate lactate* and *gluconate* are available The doses of the several salts vary with their calcium content Carbonate contains 40 per cent chloride 36 per cent lactate 18 per cent and gluconate 10 per cent of calcium Calcium chloride is most popular and is given in daily doses of 5 gm dissolved in fruit juices It causes anorexia nausea and vomiting and leads to acidosis if large doses are continued In mild cases satisfactory control is accomplished with 1 to 2 gm of lactate or carbonate or 3 to 6 gm of gluconate daily

Calcium gluconate (10 per cent) may be given *intramuscularly* or *intravenously* in amounts of 10 to 20 cc The blood calcium rise is immediate and the level remains above the tetany value for as long as 2 to 3 hours Calcium chloride may be used intravenously but it is too irritating for intramuscular use Either salt should be given slowly to minimize the sensation of heat that follows intravenous injection

Low Phosphorus Diet—A low phosphorus diet of 3 gm daily or less with a high intake of calcium aids in the control of tetany The diet is poor in meats milk cheese nuts and egg yolk and rich in fruit vegetables fats, carbohydrates and egg whites

Aluminum Hydroxide Gel—Aluminum hydroxide gel by lessening intestinal absorption of phosphorus through the formation of insoluble aluminum phosphate accomplishes the same result as a low phosphorus diet This promises to be valuable in the treatment of tetany associated with elevation of blood phosphorus

Parathyroid Extract—The use of parathyroid extract (p 1224) in the

SECTION VI

POISONING

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CHAPTER 33

POISONING

- Occupational Hazards
- Poisonous Gases and Vapors
  - War Gases
- Nongaseous Toxic Substances
  - Lead
  - Mercury

THE present section is devoted to a consideration of the noxious effects of substances that are not deliberately introduced into the human body for purposes of therapy The word poisoning is used in contradistinction to untoward effects produced by remedies administered in the course of treatment

The problem of poisoning is of increasing importance in clinical medicine In the *individual* poisoning may result from the accidental or deliberate ingestion of a harmful ingredient or the noxious substance may be administered with suicidal or murderous intent Under either circumstance the practitioner has medicolegal obligations to the authorities

Occupational poisonings have accompanied advances in industrialization The United States Department of Labor has listed more than five hundred occupations each of which involves one or more industrial hazards *Mass poisonings* with gas have been added to the armamentarium of war Civilian communities and the armed forces alike may be exposed to this menace

Poisons may best be classified as *gaseous* and *nongaseous* Vapors are inhaled whereas nongaseous substances are introduced into the body by contact or ingestion This differentiation serves a useful purpose in diagnosis and treatment

General Principles of Diagnosis —Poisoning in the *individual* often presents an intricate diagnostic problem for the practitioner The investigation requires a combination of detective work and accurate and painstaking chemical analyses Clues may be obtained from ingredients used in cosmetics or industry from the examination of substances taken in the guise of medicinal remedies and from exhaustive analyses of urines and stools Qualitative chemical tests may not be sufficient since traces of such substances as lead and mercury may be recognized under normal conditions Accurate quantitative results must be obtained to be of significant diagnostic value

Occupations involving the inhalation of volatile substances or dusts may cause acute or chronic pulmonary changes best revealed by routine radiographs In the presence of positive findings a temperature record is mandatory and sputum examinations are made for tubercle bacilli and the various mycotic invaders *Silicosis anthracosis pneumoco-*

DIFFERENTIAL DIAGNOSIS OF

Hypophosphatemia

Serum phosphate values may fall as low as 1 to 2 mg per 100 cc The clinical manifestations of this change are dependent somewhat upon the state of the calcium in the serum

CAUSE	DIAGNOSTIC FEATURES
Rickets	Vitamin D deficiency with characteristic changes in the epiphyses (p 2850) Treat with calcium and vitamin D
Osteomalacia	Adult rickets dependent upon vitamin D deficiency (p 2853)
Idiopathia Steatorrhea	Fatty diarrheas in conditions such as celiac disease and tropical or non tropical sprue Often accompanied by demineralization disturbances of growth, rickets and tetany
Hyperparathyroidism	Of primary or secondary causation (p 12-5)
Increased Carbohydrate Utilization	Particularly following injections of insulin and epinephrine

DIFFERENTIAL DIAGNOSIS OF

Increased Phosphatase Activity

Increases may be noted in both acid and alkaline phosphatase of the serum The Bodansky units are referable to the alkaline phosphatase Acid phosphatase is determined by a similar method but in a pH of 6 4 in an unbuffered sodium glycerophosphate substrate The normal values are usually less than 5 per cent of the alkaline values

CAUSE	DIAGNOSTIC FEATURES
Rickets	Values may rise to 30 Bodansky units with a decrease during the period of anti rhachitic therapy
Hyperparathyroidism	Occurs in adenomas of the parathyroid gland and in the syndrome of osteitis fibrosa cystica Normal values after adequate parathyroidectomy Increases also seen in hyperparathyroidism associated with renal insufficiency and pregnancy
Osteitis Deformans	In Paget s disease of bone with enlargement of cranium and bowing of legs Serum calcium and phosphorus values are normal
Miscellaneous Skeletal Disorders	Slight elevation in generalized osteoporosis osteomalacia metastatic skeletal carcinomatosis fractures Gaucher s disease osteopetrosis osteosclerosis and bone resorption associated with multiple myeloma Get skeletal x rays hemograms and aspirate from bone marrow (p 1043)
Biliary Tract Disorders	In obstructive and hepatocellular jaundice and biliary fistulas. Increase parallels hyperbilirubinemia
Prostatic Carcinomatosis	Increase in acid phosphatase (p 2450) Useful as index to efficacy of hormone therapy

WAR GASES

The war gases have been classified into five chief groups (1) lacrimators (2) sternutators (3) lung irritants (4) vesicants and (5) systemic toxic agents

Lacrimators.—As implied in their name lacrimators on contact with the eye produce a copious secretion of *tears* There is considerable *burning* and *blepharospasm* effecting a temporary incapacitation of the individual affected Permanent damage is rare

During the first World War over ten lacrimator gases were used The most effective lacrimating agents are *chloracetophenone bromobenzyl cyanide* and *ethyliodoacetate*

Treatment—Treatment following exposure to lacrimators is purely *symptomatic* The conjunctival sac is irrigated with copious amounts of a 2 per cent bicarbonate boric acid solution Pain can be relieved by the application of 2 per cent butyn Any of the toxic agent remaining on the skin may be removed with sodium *bicarbonate solution*

Sternutators—The sternutators irritate the upper portion of the respiratory tract and cause *nausea vomiting* and *headache* By these effects they temporarily incapacitate exposed individuals

Chemically the sternutators are derivatives of *arsine* (p 746) They depend for their effect on the passage of small particles of the toxic agent into the respiratory tract Although the immediate effects are most prominent in the *upper respiratory tract* as evidenced by sneezing and dry cough these gases have their most serious action on the trachea and bronchi where they destroy epithelium Alveolar damage is less common but irritation in the lower portions of the respiratory tract may produce *pulmonary edema*

The upper airways usually contain a thick fibrinous exudate which makes *respiration difficult Complicating infection atelectasis hemorrhage* and *emphysema* are not uncommon sequelas

Systemic effects of arsenic are uncommon At times there may be sensory and motor disturbances due to *peripheral neuritis* but changes in the visceral organs are practically never seen

Treatment—Treatment is purely symptomatic Painful mucous membrane surfaces are relieved by anesthetics applied locally or by central acting analgesics where necessary General *supportive measures* are of course undertaken as needed

Lung Irritants—*Chlorine* is a typical lung irritant gas Its toxic effects and the necessary treatment following exposure to it have been outlined in the discussion of Noxious Gas Used in Industry (p 746) Since the other members of this group act similarly the treatment following exposure to them is the same

Besides chlorine the important members of the lung irritant group include *phosgene diphosgene* and *chlorpicrin* Chlorpicrin in addition to being a lung irritant acts as a strong lacrimator and produces diarrhea nausea and vomiting

Vesicants.—The vesicants are perhaps the most dangerous of all war gases in that it is most difficult to provide adequate protection against them All exposed surfaces are liable to injury

all animal tissues and a small but definite quantity is demonstrable in normal serum which contains 1 to 4 units of activity (Bodansky) per 100 cc with slightly higher values in childhood

DISTURBANCES IN SODIUM METABOLISM

The concentration of sodium in the blood serum of normal individuals varies from 137 to 142 milliequivalents per liter (315 to 330 mg per cent) Gross deviations from these values are relatively uncommon since any tendency toward a change in serum sodium is attended by a simultaneous

DIFFERENTIAL DIAGNOSIS OF

Hypernatremia

Moderate increase in serum sodium concentration is infrequently encountered and is of minor clinical significance

CAUSE	DIAGNOSTIC FEATURES
Basophilic Adenoma of the Anterior Pituitary Gland	In Cushing s syndrome a moderate elevation is encountered and may be accompanied by urinary changes similar to those occurring in diabetes insipidus (p 1175)
Increased Adrenal Cortical Activity	As the result of neoplasms of the adrenal cortex producing the Cushing syndrome and of overdosage with desoxycorticosterone serum sodium levels may rise excessively With overdosages of hormone in Addison s disease patients develop edema due to retention of salt and water (p. 1268)
Diabetes Insipidus	Sodium not excreted at normal clearance rates in urine Tendency relieved by administration of posterior lobe anti-diuretic hormone (p. 1180)
Changes in Water Metabolism	Following water deprivation excessive sweating overloading as the result of saline infusions and too vigorous diuresis from mercurials (p 2261)

change in the water content of the blood which tends to keep the sodium value constant Significant alterations in serum sodium are usually attended by a disturbance of the plasma volume For the most part sodium determinations are of academic importance especially in view of the technical difficulties inherent in their accurate determination and the many simpler guides to changes in concentration

DISTURBANCES OF POTASSIUM METABOLISM

Normal blood serum contains comparatively small amounts of potassium The values range between 4 1 and 5 6 milliequivalents or 16 to 22 mg per cent Most of the potassium is intracellular

Bromine	Bromine and bromine salts disinfectants dyes explosives ink insecticides photography manufacture of war gases and tetraethyl lead	Intense irritation of conjunctiva and upper respiratory mucous membranes photophobia lacrimation conjunctivitis dyspnea cough and pulmonary edema	Gas of characteristic reddish brown color brownish staining of skin and mucous membranes bromine in urine	See Chlorine Poisoning (p 748)
Carbon Dioxide	Alkali salts baking blast furnaces boiler room mineral water brass foundry brewing brick making caisson construction work carbon dioxide charcoal pressing *foundry and furnace* disinfectants dyes explosives *fertilizer* fire extinguishing glue refrigerating lime burning mining pharmaceutical sewers silos sugar tannery tobacco wine making yeast manufacturing	Vertigo drowsiness headache, cyanosis dyspnea, elevation of blood pressure cardiac irregularity and collapse Solid carbon dioxide snow may produce a severe burn on direct contact	*History*	Symptomatic artificial respiration and oxygen inhalation, if necessary
Carbon Disulfide	Acetylene workers cementers of rubber shoes dry cleaners electroplaters enamel workers explosives *glue* insecticide and paint workers rayon *and* rubber workers sulfur and varnish *workers* vulcanizers	Stimulation of central *nervous* system hilarity irritability agitation hallucinations mania with later depression unconsciousness and death Chronic poisoning produces mental abnormalities peripheral neuritis atrophy of optic nerve emotional instability and *impotence*	History	Symptomatic and supportive
Carbon Monoxide	Automobile workers water gas and illuminating gas workers coal mine fires poorly vented heating stoves many other occupations	Carbon monoxide in combination with hemoglobin leaves *insufficient oxygen* carriage "cherry red cyanosis asphyxia headache flushing weakness vertigo nausea, vomiting tachycardia collapse coma convulsions respiratory depression and death	History	Artificial respiration inhalations of oxygen or 93 per cent oxygen and 7 per cent carbon dioxide

DISTURBANCES OF CARBOHYDRATE METABOLISM

In health the blood sugar level is not constant It varies from person to person and in the same individual at different times since many vari

DIFFERENTIAL DIAGNOSIS OF

Hyperchloremia

Hyperchloremia is usually associated with hypernatremia Undoubtedly the disturbances which are manifest clinically are the result of the alteration in sodium rather than in chloride metabolism

CAUSE	DIAGNOSTIC FEATURES
Renal Insufficiency	Of less importance in edematous types of nephritis than hypoproteinemia hence slight need for salt poor diets
Essential Hypertension	Rare and insignificant elevation attest to the uselessness of salt poor diets
Backward Failure	Inability to demonstrate constant relationship between edema and chloride retention attest to inadvisability of using the unpalatable salt poor diet
Excessive Chloride Administration	Particularly with intravenous infusions of more than 2 liters daily of physiological saline solution containing 9 gm per liter

DIFFERENTIAL DIAGNOSIS OF

Hypochloremia

Hypochloremia is of occasional clinical importance because of the essential role of the chloride ion in the maintenance of normal acid base equilibrium and water balance

CAUSE	DIAGNOSTIC FEATURES
Loss of Gastro-Intestinal Secretions	With excessive vomiting prolonged gastric drainage and frequent lavage withdrawal of free acid favors production of alkalosis (p 722)
Renal Insufficiency	Particularly when associated with vomiting and diarrhea With former loss of acid may prevent acidosis by shift to alkaline side
Bichloride Poisoning	Partially due to incidental vomiting and diarrhea
Diabetes Mellitus	With acidosis vomiting and polyuria
In Infection	Particularly lobar pneumonia pulmonary tuberculosis rheumatic fever and meningitis Blood chlorides probably depleted due to retention of ion in tissues
Adrenal Cortical Insufficiency	With hyponatremia in Addison s disease (p 1271)

ables may produce fluctuations Low values are encountered in children up to the age of 3 whilst higher figures are obtained in older patients who

Formaldehyde	Asbestos, brewing, manufacture of brushes, dyes, electroplating, lacquer and varnish, soap, tannery, rubber, pharmaceuticals	Inflammation of conjunctiva and respiratory passages, tearing, cough, nausea and vomiting	Odor	Symptomatic
	Pathologists	Chronic exposure of hand produces dermatitis with destruction of fingernails		
Hydrogen Sulfide	Metal workers, paper workers, dye, glue, match, fats, oils, packing house, phosphorus, rayon, soap, starch, sulfide cannery, laboratory, miners	Irritation of conjunctivae, keratitis, photophobia, rhinitis, laryngitis, bronchitis, pulmonary edema, headache, vertigo, central nervous system depression, psychic disturbances and terminal respiratory depression from tissue anoxia	History	Artificial respiration, inhalations of oxygen (93 per cent) and carbon dioxide (7 per cent), plasma infusions, as in shock (p 928)
Nitrous Fumes	Acid makers, aniline workers, artificial leather workers, bleachers, calico printers, collodion, dye, electroplating, hat etching, explosives, galvanizing, hat industries, miners, nitrate workers, nitrocellulose, pyroxylin plastics workers, welders, torch cutters, blasters	Irritation of respiratory tract, digestive disturbances, peripheral vasodilatation, methemoglobinemia, corrosion of teeth, central nervous system depression, insomnia, anorexia, asthenia, constipation, headache, ulcers of the mucous membranes	History	Symptomatic
Sulfur Dioxide	Artificial ice and refrigerator makers, blast furnace workers, bleachers, brick makers, cellulose and coke-oven workers, exterminators, fertilizer and insecticide workers, lead and mercury smelters, paper, petroleum and pyrites workers, sugar, storage battery, sulfur dioxide workers, sulfur miners, zinc smelters	Irritation of conjunctivae and respiratory tract, photophobia, lacrimation, nasopharyngitis, impairment of senses of smell and taste, exertional dyspnea	History	Symptomatic

STRIOTHALAMIC —Athetotic or choreiform movements, grimaces or compulsions

HYPOTHALAMIC —Subnormal temperature somnolence hunger thirst and vasomotor collapse

Gastro Intestinal

Hunger sinking sensation in epigastrium vomiting abdominal pain or hematemesis

Cardiovascular

Tachycardia extrasystoles hypertension and angina pectoris

Hematologic

Leukocytosis

DIFFERENTIAL DIAGNOSIS OF

Hypoglycemia

Hypoglycemia is less frequently encountered than increases in the level of blood sugar The disturbance is most commonly encountered as the result of overdosage with insulin, or failure to follow the insulin injection by a meal containing adequate quantities of carbohydrate

CAUSE	DIAGNOSTIC FEATURES
Hypothyroidism	In myxedema and cretinism with diminution of BMR (p 191)
Adrenal Cortical Deficiency	In Addison s disease with hypotension and pigmentation (p 1271)
Hypopituitarism	Particularly in pituitary cachexia (Simmonds disease) with low BMR and asthenia (p 1169)
Hyperinsulinism	Due to increased dosages of insulin failure to ingest carbohydrate following the insulin injection, or adenomatosis of the pancreas involving the islands of Langerhans (p 1242)
Hepatic Insufficiency	With depletion of hepatic glycogen in the various types of hepatitis and in the cirrhoses (p 1909)
Alimentary	Defective absorption of carbohydrate in sprue, celiac disease and idiopathic steatorrhea (p 1938)
von Gierke s Disease	Glycogen infiltrations in the newborn and flat curve of sugar tolerance (p 1978)
Anorexia Nervosa	Psychogenic disorder of younger females with asthenia, loss of appetite and diminution of BMR (p 1768)

The hypoglycemic state usually shows a progressive increase in severity and levels of symptomatology are recognized in a manner somewhat analogous to the planes of general anesthesia The stages of hypoglycemia are the following

Premonitory Stage —Fatigue lassitude malaise and restlessness

Epinephrine Stage (due to the release of epinephrine) —Fear pallor palpitation tremor cold perspiration hunger and thirst

Intoxication Stage (resembles alcoholic intoxication) —Hallucinations compulsions fugues and incoordination

elapses between exposure and institution of therapy The earlier procedures are begun the more effective will be the effects

With *mustard gas* the skin is cleansed with kerosene gasoline without lead alcohol or an oily substance Clean cloths and fresh kerosene are used and discarded every few minutes when they become contaminated with the gas Decontamination is continued for twenty to thirty minutes and is followed by a thorough cleansing bath of hot water and tincture of green soap *If the solvents mentioned above are not available oxidizing* agents may be used These include (*1*) bleaching powder (chloride of lime) made into a paste with an equal amount of water (*2*) sodium hypochlorite solution 0.5 per cent (*3*) hydrogen peroxide solution 2 to 3 per cent (*4*) potassium permanganate solution 1 1000 to 1 10 000 or (*5*) chlorinating agent as chloramine T solution 1 to 2 per cent The *oxidizing* and chlorinating agents convert the mustard gas into compounds which are not noxious for the skin and mucous membranes

The eyes and the accessible mucous membranes are washed with a warm solution of boric acid 2 or 3 per cent sodium bicarbonate or physio*logical* saline solution Sterile petrolatum or castor *oil is then instilled* into the conjunctival sac and the pupil is dilated with 1 per cent atropine sulfate

After these procedures are finished the skin is treated with a soothing agent such as lotion of calamine and zinc Ointments are undesirable but *the sulfadiazine triethanolamine mixture recommended for burns* (*p 3128*) may be useful as a preventive against secondary pyoderma Sulfathiazole or sulfadiazine may also be given by mouth to protect against pyoderms and bacterial invasion of inflamed mucous membrane and lung tissues

In the case of *lewisite burns* the urgency for immediate first aid treatment *is extremely great To minimize the absorption of arsenic* the skin is sponged liberally and thoroughly with a 5 per cent solution of sodium hydroxide this is followed by a cleansing bath of warm water and tincture of green soap Where there are severe localized burns due to liquid lewisite the area is excised and healing often takes place by primary union after *suturing* After the cleansing bath *a layer of ferric* hydrate paste is applied covered with sterile gauze and oiled silk or some other impervious material and left in place for twelve hours When blisters develop they should be evacuated promptly since they may contain unabsorbed arsenic The after treatment is similar to that of mustard burns

NONGASEOUS TOXIC SUBSTANCES

The more important nongaseous toxic substances include antimony *arsenic cadmium calcium chloride calcium* cyanamide *carbon tetrachlo*ride chromium dinitrophenol fluorine hydrochloric acid lead manganese mercury metal fumes methyl alcohol naphtha nickel nitrobenzol phenol and cresol phosphorus radioactive substances selenium silver sulfuric acid tellurium tetraethyl lead thallium trichlorethylene toluol turpentine xylol and zinc

Certain of these products notably arsenic and mercury are employed therapeutically under which circumstance untoward effects occasionally result from overdosage or idiosyncrasy These reactions are not the concern of the present discussion which is limited to the effects that occur in poisoning deliberate or intentional or as an industrial hazard

Hypoproteinemia has received previous consideration in the material that is devoted to the problem of edema (p 706) Concentrations in excess of 8 gm per cent constitute hyperproteinemia usually associated with a reversal of the albumin globulin ratio

Hyperproteinemia in contrast to hypoproteinemia is relatively infrequently encountered An increase in the amount of plasma albumin is almost never the cause of a hyperproteinemia In most instances the in

DIFFERENTIAL DIAGNOSIS OF

Hypercholesteremia

An increase in total blood cholesterol usually indicates an increase in the concentration of blood lipids As a general rule elevations are due to endocrine disorders or to abnormalities in the blood proteins

CAUSE	DIAGNOSTIC FEATURES
Hypothyroidism	Increase in plasma cholesterol in myxedema and cretinism is in inverse proportion to diminution in BMR Blood chemical determinations have the advantage over BMR determinations in that patient-cooperation is not required and an objective test is made available Note effects of therapeutic test with extract (p 1189)
Hypoinsulinism	In untreated and severe diabetes mellitus The plasma may be milky and cholesterol values may exceed 1000 mg Persistent hypercholesterinemia carries a bad prognosis since many patients suffer from arteriosclerosis gangrene and cataract formation
Nephrosis	Hypercholesterinemia bears a constant and inverse relationship to hypoproteinemia. As in hypothyroidism retention of lipid is associated with depression of the BMR (p 719)
Hepatic Insufficiency	With biliary obstruction, increases involve both free and ester fractions of the cholesterol content. A fall in the cholesterol ester is an important prognostic sign, indicating hepatocellular degeneration
Xanthomatosis	With disturbances of the reticulo-endothelial system such as cutaneous xanthomata Gaucher s disease and Schuller Hand Christian syndrome (p 1135)

crease is due to excessive amounts of globulin and more specifically in the euglobulin rather than the pseudoglobulin moiety A medical curiosity of indefinite clinical significance is the condition of *hyperinosis* resulting from a rise in plasma fibrinogen

Hyperglobulinemia with Reversal of Albumin Globulin Ratio—With hyperglobulinemia a number of curious and apparently unrelated clinical phenomena are encountered These include rouleau formation with clumping of the red blood cells agglutination of erythrocytes after transfusion of

Cadm um	C l r n k s l ctio l t rs gl colorers lead melte metal rs sol d r m kers stora e battery makers text le p inters wel lers zinc smelters refiners	D yn s of tl t co gh t gl tness of l est dyspnea pulmona y nfl at on an re a gastro intest nal d turb ances asthenia tachyca d a renal ir ritat on n etal fume fever	H tory	S mpto nat c
Calcium Chloride	Acet lene workers bleache s bleach ng powder makers button makers cl lo ride of lime wo kers chloroform work ers dis nfectant makers dye makers laundry orkers pharmaceutical ork e s straw l at makers tan ery work ers ater pu fiers	e Cl l r ne (Tal le 49)	History	Symptomatic
Calcium Cyanamide	Ammonia workers cyanide manufac turers farmer makers of fertilizer employees in pharmaceutic manufac ture	Severe irritat ons of upper respiratory t act and skin alcohol cs d velop h adache va od latation hypotensio and tacl y cardia	History	Symptomatic
Carbon Tetrachloride	A rplane dope workers a rplane hangar employees metal burnisl ers carbon *tetrachloride* workers rubber cement kers chloroform makers c bblers dry cleaners dye makers electroplat ers fire extinguisher makers leather workers l noleum makers perfume and paraffin workers pharn aceut cal worl ers polish mal ers printers plas t cs workers soap makers vul anizers waterproof fabric makers	Irritation of eyes and upper resp ratory tract headache and vertigo visual ab normalities anorexia nausea and omiting diarrhea torpor narcosis xcitement confusion nervousness hyperchromic macrocytic anemia jaundice uremia and death	History	Intravenous injections of calcium gluconate (p 601) high carbo l ydrate high calcium diet

DIFFERENTIAL DIAGNOSIS OF

Hypocholesteremia

Hypocholesteremia is infrequently encountered except in hyperthyroidism where it has both diagnostic and prognostic significance

CAUSE	DIAGNOSTIC FEATURES
Anemia	Particularly in hyperchromic variety Get hemogram (p 1055)
Hepatic Insufficiency	Diminution in ester fraction of diagnostic and prognostic significance in hepatocellular degeneration (p 1970)
Hyperthyroidism	Usually blood cholesterol falls in inverse proportion to the rise in BMR. Chemical test, being objective is more accurate and furnishes indication for prognosis and the success of therapy Note effect of iodide (p 1213)
Inanition	Diminution of plasma cholesterol accompanies wasting and cachexia.

DIFFERENTIAL DIAGNOSIS OF

Hyperlipemia

Increase in total blood fat may produce a characteristically opaque and milky serum which is heavily laden with fat globules The content of cholesterol may or may not parallel the increase in neutral fats Persistent hyperlipemia is associated with the deposition of yellowish plaque like deposits in the subcutaneous tissues carotine like yellow discrete papules which appear and disappear rapidly and which are most common on pressure points eruptive xanthomas starting as vesicle but soon becoming ulcerated, a diffuse yellow stain to he skin of the hands and the feet (xanthosis) and intense itching

CAUSE	DIAGNOSTIC FEATURES
Alimentary	Follows fatty meal
Idiopathic Familial Hyperlipemia	Associated with hepatosplenomegaly and nodular xanthomatous eruptions
Hypo insulinism	Diabetic hyperlipemia occurs in poorly controlled diabetics May be associated with xanthelasma xanthomas arteriosclerosis gangrene and cataract formation (p 1246)
Pancreatic Deficiency	In acute and chronic pancreatitis (p 1937) Associated with hepatomegaly and xanthomatosis
von Gierke s Disease	Associated with infantile metabolic disorder characterized by the deposition and storage of large amounts of glycogen Sugar tolerance test is flat and acetonuria is persistent. Hepatomegaly is marked (p 1978)
Nephrosis	Lipemia may or may not parallel hypercholesterinemia.

Flu n	Alum num work rs antim ny fluo d wo kers art glass wo kers bleach rs brev e s b kmakers copp r workers dyers electroplaters enamel makers fertil zer makers gas-workers glass etchers and finishers gold refiners hy d ofluoric acid makers paper makers phosphorus workers pottery workers welders yeast makers	*Acute expo e causes* yth ma, b rn ing of kin conjun tiva and resp ra to y mucous membranes ulceration of nostrils gums o al mucosa and cuticle suppurating subungual vesicles Following accidental ingestion there appear nausea, salivation abdominal pain vomiting diarrhea, convulsions respiratory depression and death *Chronic po soning* produces mottling of the teeth gastro-intestinal disturbances cachexia and neurological mani festations	H tory	Of cute poison ng gastric lav ge wit l im water or milk *Chronic poison ng* is treated symptomatically
Hydrochloric Acid	Acid dippers ammonium salt makers anil ne workers battery makers bleachers chlorine manufacturers dye makers electroplaters electroengravers etchers fertilizer makers glass workers pottery workers glue makers jewelers leather workers paint makers paper mill workers synthetic perfume makers photographic workers soap makers sugar refiners tannery workers textile printers	See Sulfuric Acid	History	See Sulfuric Acid
Lead		See p 62		Try BAL (p 6)
Manganese	Alloy makers aluminum extractors dry battery makers bleaching powder makers brickmakers chlorine makers copper smelters dye makers enamel makers fertilizer makers fireworks makers glass and pottery workers linol um makers manganese-dioxide workers match factory workers painters and paint makers pharmaceutical workers iron and steel puddlers soap makers varnish makers welders zinc w rk rs	Suggest progressive hepatolenticular degeneration masklike facial expression monotonous speech intention tremor muscle cramps stiffness increased tendon reflexes retropulsion and propulsion hyperemotionality "metal fume fever	History	Symptomatic

Nitrobenzol Dinitro-benzol and Trinitro-toluol	Anilin workers cosmetic makers dinitrobenzol workers dye makers explosives makers floor polish makers gasoline blenders glue workers ink makers nitrators nitrobenzol workers perfume makers petroleum refiners polish makers shell fillers shoe dyers smokeless powder makers soap makers trinitrotoluol makers	Cyanosis somnolence vertigo headache nausea, vomiting bitter almond odor to breath ataxia twitching tremor visual disorders methemoglobinemia anemia hematoporphyrinuria and dermatitis	History	Symptomatic
Phenol and Cresol	Coal tar workers cresol soap workers disinfectant makers dye and paint remover makers explosives workers glue workers ink makers insecticide makers synthetic perfume makers photographic workers	Ingestion causes severe abdominal pain vomiting shock transitory excitement convulsion unconsciousness respiratory depression and renal damage Inhalation causes irritation of the upper respiratory passages and chronic exposure leads to anorexia, vomiting diarrhea cachexia headache vertigo hepatic and renal insufficiency and circulatory disturbances	Odor	Gastric lavage for acute poisoning with retention of olive oil intravenous plasma for shock artificial respiration if necessary Local contact may be alleviated by washing with castor oil or 50 per cent alcohol
Phosphorus	Bone black makers brass founders explosives workers exterminators fire works makers insecticide makers match factory workers pharmaceutical workers phosphorus workers and elders	Acute poisoning causes abdominal pain nausea vomiting diarrhea garlic odor to breath shock enlargement and tenderness of liver jaundice cardiac depression renal irritation albuminuria cylindruria hematuria, oliguria hemorrhagic tendency coma delirium and death Chronic exposure causes necrosis of jaws and facial bones (phossy jaw) toothache anorexia swelling of gums difficulty in swallowing renal and hepatic damage	History	Gastric lavage with 1 per cent potassium permanganate for acute poisoning intravenous plasma for shock artificial respiration high carbohydrate diet

Sulfuric Acid	Acid dippers and finishers alum workers ammonium salt makers artificial leather makers brewery workers candle makers carbolic acid makers cellulose makers color makers dye makers electroplaters and engravers etchers explosives workers felt hat workers fertilizer makers glue makers hydrochloric acid makers jewelers linoleum makers lithographers nitric acid makers nitroglycerin and nitrocellulose makers oil purifiers paint makers perfume makers petroleum refiners pharmaceutical workers phenol makers phosphoric acid makers photographic workers picric acid workers pyroxylin plastics workers rayon makers metal refiners soap makers soda makers storage battery workers sugar refiners sulfuric acid makers cannery workers textile printers	Corrosive effects on skin mucous membranes eyes and respiratory tract ingestion produces severe gastro intestinal irritation with vomiting hematemesis ulceration and perforation of bowel	History		Gastric lavage opiates intravenous infusion of plasma laparotomy for perforation
Tellurium	Copper refiners lead refiners pharmaceutical workers	Garlic odor to breath suppression of sweat dryness of mouth itching dryness of skin anorexia, constipation vomiting and insomnia	History		Symptomatic
Tetraethyl Lead	Gasoline makers and handlers	Anorexia nausea vomiting vertigo headache insomnia weakness hypotension hypopyrexia weight loss pallor and abdominal cramps	History		Symptomatic

niosis and *asbestosis* (p 2065) furnish sites of least resistance for invasion by the tubercle bacillus

The acute effects of physical injuries are elsewhere discussed Excessive heat and profound changes in barometric pressures may cause serious clinical disturbances

See *Effects of Heat* (p 3981)
Effects of Cold (p 3982)
Caisson Disease (p 1501)
Effects of Altitude (p 926)

A chart appears on p 746 which has been prepared from Bulletin 41 of the United States Department of Labor It is a summary of the occupational hazards and the diagnostic features of disturbances caused by them grouped in a manner that will prove serviceable to the practitioner not primarily engaged in industrial medicine

General Principles of Treatment —The most important therapeutic principle in occupational disturbances is that of prophylaxis In almost all instances safety devices have been introduced for the protection of the worker It is part of the duty of the physician to see that individual neglect is remedied by educational methods and that neglect on the part of the employer is reported to State or Federal labor authorities

Should the occupational hazard prove a continuing threat to the health of the worker a change of job is recommended The patient is advised then to investigate the possibility of receiving the compensation to which he is entitled under the law

OCCUPATIONAL HAZARDS

Many of the occupational hazards have been elsewhere described For further descriptions of these conditions the reader is referred to abnormalities due to *increased atmospheric pressure* (p 1501) and *decreased atmospheric pressure* (p 926) abnormalities due to temperature particularly *heat* (p 3981) the pulmonary deposits due to the inhalation of the various dusts infections which are prone to occur in the pursuit of certain occupations such as *tularemia* (p 322) in those who handle rabbits *brucellosis* (p 314) in farmers *pulmonary fungous infections* (p 499) in those exposed to dust and implantations of *tuberculosis* in miners and others who work under unfavorable hygienic conditions

Many of the poisons produce mere chemical irritation These include such substances as *acetaldehyde acetone acridine acrolein butyl alcohol ethylene* and *ether derivatives volatile acids* and *naphthols* Others produce local dermatoses as described in the section on *Contact Dermatitis* (p 3330) A relatively small number of volatile and non volatile preparations are capable of the production of quite definitive symptoms they are discussed in the following paragraphs

POISONOUS GASES AND VAPORS

The poisonous gases and vapors include ammonia arsine benzine benzol bromine carbon dioxide carbon disulfide carbon monoxide chlorine cyanogen formaldehyde hydrogen sulfide nitrous fumes sulfur dioxide and the war gases which include lacrimators sternutators lung irritants and vesicants

Turpentine	Art glass wo kers camphor mak rs rub ber workers compos t rs pottery decorators dry-cleaners dye makers enamel rs and enamel makers feather workers furn ture pol sl ers ink mak ers insecticid makers lacquer mak ers linoleum makers l th ographers millinery workers pa nters and paint makers patent l ather makers petroleum ref nery workers pharmaceutical wo kers photographic workers polish ers and pol sh makers printers seal in wax makers shellackers and shellac makers shoe factory operators textile printers varnishers varnish mak rs wax makers	I r t n of skin mucous m mb anes of re p atory and d g st ve tracts photophob a lacrimation salivati n h adache vomiting abdominal pain vert go ineb ation renal and bla ld r irritation and st angury	U e has odor of v o l ts	G t e l vag st anal to ed oth r ymptomat c
Zinc	Z nc smelters b ass founders galvan izers junk metal ref ners welders	Abdominal cramps nau ea vomiting metal fume fever	H s tory	Symptomatic

TABLE 49.—CLINICAL MANIFESTATIONS, DIAGNOSIS AND TREATMENT OF POISONING FROM GASES AND VAPORS

Substances	Occupations	Clinical Manifestations	Diagnostic Features	Treatment
Ammonia	Acetylene, ammonia and ammonium salts, refrigeration, calcium carbide, plastic and rubber cement, coke ovens, cyanides, dye, electrotyping, explosives, fertilizer, illuminating gas, glue, ink, lacquer and shellac, mirror, nitric acid, paper, perfume, petroleum, photography, rayon, soda, sugar, tannery, vulcanizing	Intense irritation of skin, eyes and mucous membranes of upper respiratory tract, photophobia, lacrimation, cough, dyspnea, bronchitis and pulmonary exudation	Odor of gas	Symptomatic, local anesthetic for eye
Arsine	Acetylene and aniline factories, manufacture of bleaching powder, rayon, electrolytic processes (storage batteries, handling of sulfuric acid)	Depression of central nervous system and hemolytic anemia, chills, fever, lumbar pain, albuminuria, hemoglobinuria, hematuria, oliguria and jaundice of prehepatic type	History, arsenic in urine	Hematinics, intravenous infusions of plasma and blood, dimercaptol (BAL) (p 767)
Benzine	*Gasoline engines*, electroplating, rubber cement, printing, pottery, tanning, glue, ink, insecticides, paint, lacquer, polish, linoleum, lithography, pyroxylin plastics, rubber shoes, soap, window shades, wood	Depression of central nervous system, headache, vertigo, abdominal pain, nausea, vomiting, irregular respiration, irritation of skin and mucous membranes, convulsions, stupor	History	Symptomatic, artificial respiration and oxygen inhalations if necessary
Benzol (Benzene)	Airplane dope workers, alcohol and aniline makers, auto painters, beauty parlor technicians, benzol workers, rubber cementers, coal tar workers, dry cleaners, engravers and electroplaters, manufacture of explosives, fertilizers, gas, lacquer, linoleum, lithograph, millinery, mirrors, nitrocellulose, paints, pencils, perfumes, petroleum, pharmaceuticals, photographs and polishes, printing, rubber tire, shellac, shoes, soap, t n t, nitrotoluol, varnish, war gas and window shades, welding	Stimulation of central nervous system, excitation, convulsions with later depression, coma and respiratory failure, depression of bone marrow with thrombocytopenia, granulopenia and erythropenia	History	Hematinics, repeated transfusions, pentnucleotide (p 1100)

deposition of lead Conversely factors leading to decalcification (p 280a) *bring about the liberation of lead deposited in the skeleton*

Clinical Features—Lead affects the nervous gastro intestinal and hematopoietic systems The patient is usually pale even in the early stages before marked anemia has set in He generally appears older than his stated age and is excitable easily embarrassed and moody If jaundice appears it is usually late in the course of the disease because it depends on increased hemolysis

The Lead Line—The lead line is seen in only 50 per cent of cases It is a dark linear deposit in the gums near their junction with the teeth Other metals may produce the same line (e g silver mercury bismuth iron)

The lead line develops in the presence of poor mouth hygiene It results from putrefaction and the release of hydrogen sulfide The line is composed of *lead sulfide* which is precipitated when lead comes in contact with hydrogen sulfide Hence patients with clean mouths may have absorbed enough lead to produce poisoning without showing any lead line at all The same holds true for the edentate

Effects on Nervous System—Irritability insomnia headache and *vertigo* are important early evidences of lead intoxication Later *tremor* and *fine fibrillary twitching of the face and upper extremities* are noted At first the reflexes are hyperactive Later they become depressed Eventually *lead palsies* affecting the peroneal and radial nerves appear These cause *wrist- and foot drop* More widespread changes including *cranial nerve palsies optic neuritis* and *lead encephalopathy* may be seen in severe poisoning In addition the deltoid biceps long supinator and brachialis anticus muscles become involved Indefinite *joint and muscle pains* are common

Lead encephalopathy produces the symptoms of *increased intracranial pressure* attended by *hallucinations delirium convulsions meningismus* and *coma* Adults rarely develop this dramatic symptom complex but in children it may be the presenting manifestation of ill health

Effects on Digestive Tract—Anorexia constipation and *metallic taste* occur early Later they become more intense and are associated with *coating of the tongue* and *slight abdominal colic* In advanced cases *nausea vomiting* and *severe colic* make their appearance *Blood in the stool* may lead to confusion in the differential diagnosis

Renal Effects—Lead causes renal irritation manifested by *albuminuria cylindruria* and *hematuria* A form of *renal glycosuria* (p 1262) has been encountered in children with lead poisoning

Blood Changes—Early signs of lead poisoning include a *mild polycythemia polychromatophilia increase in platelets* and *reticulocytes* The reticulocyte increase is an early sensitive sign of lead intoxication Later there are evidences of bone marrow depression including *anemia increase in basophilic cells increase in mononuclears anisocytosis poikilocytosis nucleated red blood cells* and *thrombocytopenia*

In no other disease are *stippled cells* found in such numbers in the absence of other major blood changes In acute cases stippling is an early sign but in chronic cases basophilia and reticulocytosis precede stippling Stippled cells are juvenile red blood cells and are but one variation of

TABLE 49.—CLINICAL MANIFESTATIONS, DIAGNOSIS AND TREATMENT OF POISONING FROM GASES AND VAPORS (*Continued*)

Substances	Occupations	Clinical Manifestations	Diagnostic Features	Treatment
Chlorine	Alkali salt makers, bleachers, makers of bleaching powder, chloride of lime and chlorine processers, dye and ink workers, laundry workers, paper makers, photographic workers, rayon makers, textile printers, sewage purifiers, sodium hydroxide makers, sugar refiners, water gas makers, water purifiers	Irritation of eyes and respiratory mucous membranes, photophobia, lacrimation, pain in larynx and chest, cough, pulmonary edema, venous engorgement, cyanosis, acidosis, *syncope* and death. Late sequels may be emphysema, chronic bronchitis, dental decay or tuberculous implantation	History and odor of gas	*Boric acid* soaks for conjunctiva, alcohol vapor inhalations, analgesics and narcotics, phlebotomy in presence of systemic venous engorgement, intravenous infusion for shock, oxygen inhalation for respiratory distress
Cyanogen	Art printing, blacksmithing, blast furnace working, coal tar manufacture, cyanogen manufacture, dyers and dye manufacturers, electroplaters, fertilizers, illuminating gas workers, insecticides, jewel making, mirror making, photography, certain types of plastics, rayon, tannery, textiles	Cellular respiratory enzyme inactivated causing tissue anoxia, irritation of mucous membranes, eruptions, vertigo, nausea, vomiting, diarrhea, dyspnea, *palpitation*, muscle cramps, convulsions, unconsciousness and terminal asphyxia	*Bitter almond odor* to breath and chemicals	*Inhalations of amyl* nitrite for 30 seconds every 2 minutes, intravenous injections of 0.3 to 0.5 gm of sodium nitrite in 10 cc *of distilled water by slow introduction*; this followed by 25 gm *of sodium* thiosulfate in 50 cc of distilled water, alternating at 10 minute intervals with sodium nitrite; intravenous injections of methylene blue, artificial respiration, inhalations of oxygen

objective the removal of lead from the circulation and the parenchymatous organs The administration of a *high calcium and phosphate diet* and *vitamin D* promotes storage of the metal in the skeleton where it is physiologically inert The stored lead remains innocuous unless returned to the circulation by the development of *acidosis* Under such circumstances *tertiary lead phosphate* is again mobilized and acute plumbism may result

Some clinicians favor deliberate *de leading* by the use of low calcium high phosphate diets and the administration of an acidifying salt *Patients should be de leaded only if their hemoglobin is over 80 per cent* the stippled cell count less than 5000 per 1 000 000 red cells and the urinary lead excretion less than 0 15 mg per day The patient should be in good general condition

To accomplish de leading calcium and phosphate are given in the ratio of 1 4 *The patient takes 8 to 10 gm of ammonium chloride per day in* hourly divided doses to act as an acidifying agent Treatment is stopped temporarily if symptoms of lead poisoning recur In any case it seems best to rest the patient after three weeks of de leading and complete the process later if necessary

Because the body slowly loses lead spontaneously there seems to be less justification for the de leading technic which entails the danger of provoking a further attack of plumbism

Lead Colic—For the relief of lead colic vasodilator and smooth muscle relaxant substances such as *amyl nitrite* are used If these fail large doses of *atropine sulfate* are tried The intravenous injection of 10 or 15 cc of a 5 per cent solution of *calcium chloride* over a 5 minute period may produce dramatic relief

When the acute symptoms have been controlled an attempt should be made to remove the lead from the circulation by giving large amounts of *calcium* (1 to 2 quarts of milk and 3 gm of calcium lactate per day) After the patient has recovered sufficiently the decision concerning de leading is debated

Anemia—Secondary anemia should be treated with hematinics and if necessary transfusion

Peripheral Neuropathy—Peripheral neuropathy is difficult to treat It may be benefited by large doses of *thiamine chloride* given by intravenous or intramuscular injection in 25 to 100 mg amounts daily or every other day depending on the severity of the neural symptoms

Constipation—The severe constipation often seen with lead poisoning should be treated *symptomatically* with saline cathartics

Above all the patient who is receiving treatment for lead poisoning should be removed from the source of his intoxication

Mercury

Acute poisoning with mercury may be accidental or deliberate In the latter instance the purpose is often suicidal *Chronic intoxication* occurs as an industrial hazard

Hazards of industrial exposure to mercury exist *for the following* Chemical workers employed in the manufacture of acetaldehyde acetic acid acetone alcohol chlorine cyanogen disinfectants fulminate amal

TABLE 49 —CLINICAL MANIFESTATIONS DIAGNOSIS AND TREATMENT OF POISONING FROM GASES AND VAPORS (*Continued*)

Substances	Occupations	Clinical Manifestations	*Diagnostic Features*	Treatment
Chlorine	Alkali salt makers *bleachers* makers of bleaching powder chloride of lime and chlorine processers dye and ink workers *laundry* workers *paper* makers photographic workers rayon makers textile printers sewage purifiers sodium hydroxide makers sugar *refiners* water gas makers water purifiers	Irritation of eyes and respiratory mucous membranes photophobia lacrimation pain in *larynx and chest* cough pulmonary edema venous engorgement cyanosis acidosis syncope and death *Late sequels may* be emphysema chronic bronchitis dental decay or tuberculous implantation	History and odor of gas	Boric acid soaks *for conjunctiva* alcohol vapor inhalations analgesics and narcotics phlebotomy *in presence* of systemic venous engorgement intravenous *infusion for shock* oxygen inhalation for respiratory distress
Cyanogen	Art *printing blacksmithing* blast furnace working coal tar manufacture cyanogen manufacture dyers and dye manufacturers *electroplaters fertilizers* illuminating gas workers insecticides jewel making mirror making photography certain types of plastics rayons tannery textiles	Cellular respiratory enzyme inactivated causing tissue anoxia irritation of mucous membranes eruptions vertigo nausea vomiting diarrhea dyspnea palpitation muscle cramps convulsions unconsciousness and terminal *asphyxia*	*Bitter almond odor* to breath and chemicals	*Inhalations of amyl* nitrite for 30 seconds every 2 minutes intravenous injections of 0 3 to 0 5 gm of *sodium nitrite* in 10 cc of distilled water by slow introduction *thus followed by* 2.5 gm of sodium thiosulfate in 50 cc of *distilled water alter*nating at 10 minute intervals with sodium *nitrite* intravenous injections of methylene blue artificial respiration and inhalation of oxygen

the mercury *Gastric lavage* with large amounts of fluid is then under taken

In addition to these nonspecific measures the use of *sodium formaldehyde sulfoxalate* may be helpful Of the drug 250 cc of 5 per cent solution are used as a lavage A similar amount is left in the stomach after the completion of the washing In addition the patient receives 10 gm in 100 or 200 cc of fluid by intravenous infusion over the course of twenty minutes *This may be repeated in four to six hours if necessary*

The introduction of dimercaptol (BAL) has greatly enhanced the chances for recovery in both acute and chronic mercury poisonings The method is described in the paragraphs immediately following

DIMERCAPTOL (British Anti Lewisite BAL)

The chemical 2 3-dimercaptopropanol developed for local decontamination and treatment of arsenical blister gas is effective also in systemic treatment of arsenical and probably mercury poisonings

BAL owes its activity to the formation of a stable combination with arsenic thus abstracting the poison from the tissues and *permitting rapid excretion of the BAL-arsenic combination*

BAL is available in 10 per cent solution in peanut oil The recommended dose is 3 mg per kg (3 cc for a weight of 150 pounds) injected intramuscularly every four hours for the first two days every six hours on the third day and twice daily thereafter for at least ten days These amounts suffice for arsenic poisoning particularly that following arsenotherapy (p 116)

In mercury poisoning *larger doses are needed* The initial recommended dose *is 5 mg per kg followed in one or two hours by 2.5 mg per kg* After a lapse of two to four hours another dose of 2.5 mg per kg is advised with repetition in severe poisonings in 8 to 10 hours and again on the second and third days These larger doses may produce nausea vomiting headache a burning sensation in the lips lacrimation salivation myalgias anxiety and chest constriction These untoward effects usually disappear within 30 to 90 minutes The efficacy of dimercaptol already is firmly established in *hemorrhagic encephalopathy* (p 124) *exfoliative dermatitis* (p 3383) agranulocytosis (p 1096) hepatitis (p 1064) *and acute mercury poisoning* (p 766)

Although a number of vesicants have been devised *mustard gas* (*di-chlorethyl sulfide*) and *lewisite* (*β chlorovinyldichloroarsine*) are the two most widely used gases in this group

Mustard gas is peculiarly dangerous because of its delayed action on the skin Furthermore it penetrates such protective materials as rubber and leather It acts by hydrolysis to produce hydrochloric acid and it is this which is considered to be the actual noxious agent

Mustard gas is a heavy dark brown oily liquid having the odor of garlic or mustard It vaporizes more rapidly in warm weather The skin may be damaged by contact with the liquid or the colorless vapor; the effects of the liquid are much more severe and rapid than those of the vapor

After exposure there is a usual latent period of two to six hours but the symptoms may be delayed for eight to twenty four hours The rapidity of the onset of skin changes is determined chiefly by the condition of the gas being hastened when it is in liquid form, and delayed when in the gaseous form The concentration of the gas on the skin is also a determining factor Individual tolerance differs considerably the skin of the Negro being far more resistant than that of the white person

The patient complains first of burning and itching of the skin lacrimation photophobia and irritation of the eyes Systemic symptoms may be mild or completely absent and are roughly proportionate to the severity and extent of the burn In the worst cases there may be fever headache malaise prostration leukocytosis and polynucleosis A marked increase in the polymorphonuclear leukocytes is a poor prognostic sign General symptoms are more common when there is involvement of the lower respiratory passages and the lungs

The cutaneous manifestations include erythema succeeded by vesicles and bullae As the vesicles and bullae rupture eroded moist surfaces are produced These may heal without the formation of scars but residual brown pigmentation is common In exceptional instances usually due to liquid gas deep lacerations may result and these always terminate in scars Secondary pyogenic infection of the skin is often observed The conjunctiva may be inflamed keratitis and corneal opacities with impairment of vision may develop Severe membranous and necrosing inflammation of the nose mouth and throat also occur at times

Lewisite is irritating to the skin and also of high systemic toxicity The cutaneous reaction appears after a latent period of only 15 to 30 minutes and is more intense than with mustard gas Lewisite is a dark brown oily liquid which changes slowly into a colorless gas and has the odor of geraniums In addition to its capacity to burn tissues it liberates arsenic so that acute arsenical poisoning may result Like mustard gas it may attack the skin the eyes and the mucous membranes of the mouth respiratory tract and lungs and bring about similar inflammatory reactions

Treatment—Prior to the development of dimercaptol (BAL) the treatment of gas poisonings was arduous and unsatisfactory The present routine (p 767) both simplifies and improves the therapeutic program Those who handle gassed patients must wear masks and special clothing as protectives against secondary gassing

The success of prophylactic treatment depends up[illegible] time that

SECTION VII

THE CIRCULATORY SYSTEM

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ARTHUR W SELIGMANN M D

TABLE 50.—CLINICAL MANIFESTATIONS, DIAGNOSIS AND TREATMENT OF POISONING FROM NONGASEOUS TOXIC SUBSTANCES

Substances	Occupations	Clinical Manifestations	Diagnostic Features	Treatment
Antimony	Antimony refiners, babbit *metal* workers, brass founders, color makers, paint makers, dye *makers*, *electroplaters*, electrotypers, enamel makers, explosives makers, *glass mixers*, pottery makers, metal and rubber grinders, *lead smelters*, *linotypers*, match factory workers, rubber workers, pewter *workers*, *pharmaceutical* workers, printers, solder makers, storage battery *makers*, *textile printers*, type founders, vulcanizers, zinc refiners	See Arsenic	See Arsenic	See Arsenic. Try dimercaptol (BAL) intramuscularly (p. 767)
Arsenic	Arsenic workers, artificial flowers and artificial leather workers, glass making, candle making, canning, carpet making, Portland cement making, chimney sweeping, color making, rubber makers, copper workers, cosmetic workers, tannery workers, pottery workers, dye makers, electroplaters, exterminators, farmers, fertilizer manufacturers, paint makers, lacquer makers, varnish and enamel makers, fly paper makers and fireworks makers, galvanizers, ink, insecticides, iron and steel workers, lead smelters, lithographers, *painters and paperhangers*, pharmaceutical workers, pitch workers, metal refiners, silver mines, soap makers, tree sprayers, sulfuric workers, tar workers, printer, toy makers, weld[illegible]	*Acute poisoning* produces dysphagia, pain in stomach, vomiting, diarrhea, oliguria, albuminuria, hematuria, cylindruria, dehydration, muscle cramps, shock and death. *Chronic arsenic poisoning* results in asthenia, constipation, diarrhea, rhinitis, stomatitis, jaundice, loss of hair and nails, bronzing of skin (arsenic melanosis) and garlic odor to breath	Increased amounts of arsenic in urine	*Of acute poisoning*: gastric lavage and saline *catharsis to eliminate* poison, with intravenous *saline and plasma* to maintain blood *volume*, *opiates*, injections of BAL (p. 767). *Chronic poisoning* is *treated symptomatically*, sodium thiosulfate as a specific antidote is disappointing [illegible]

CHAPTER 34

PHYSIOLOGY

The circulatory system consists of a two-cylinder pump and a closed system of cylindrical tubes in which blood flows according to the principles of hydrodynamics The central pump is the heart the peripheral tubular system is made up of arteries capillaries and veins

Most clinical disturbances of the circulatory system are the results of derangements in function which may or may not have an organic basis most problems are only secondarily concerned with morphological changes which are almost invariably irreversible and irremediable

Much of the therapeutic nihilism of the early years of the twentieth century rested on the discouraging appearances of dead house material pathologists *entertained a justifiable scorn for therapeutic efforts directed* at the correction of valvular deformities arteriosclerotic thickenings aneurysmal dilatations or myocardial scars The school of cardiac physiologists led by Mackenzie and Lewis breathed new hope and vitality into the clinical problems of circulatory disease These investigators demonstrated the importance of work efficiency whether in intact or damaged structures their views brightened the prognosis of cardiac disease and aided the practitioner to sustain the patient in his normal pursuits To follow the leadership of these great clinicians the physician is required to review the physiologic principles of the circulation and apply what has been learned to the particular problem of each of his patients

THE HEART

The heart is a musculomembranous sac which contains four chambers Its muscle fibers possess longitudinal striations and transverse hatchings they communicate one with the

TABLE 50—CLINICAL MANIFESTATIONS DIAGNOSIS AND TREATMENT OF POISONING FROM NONGASEOUS TOXIC SUBSTANCES (*Continued*)

Substances	Occupations	Clinical Manifestations	Diagnostic Features	Treatment
Chromium	Acetylene workers aniline workers artificial flower makers dry battery makers bleachers colored candle makers chrome workers of all sorts color makers rubber workers dye-makers electroplaters enamel and paint workers explosives workers furniture polishers pottery workers paint makers linoleum workers book wrappers lithographers match workers paperhangers paper makers colored pencil makers photoengravers photographic workers steelmakers tannery workers textile printers vulcanizers waterproofers welders	Vomiting abdominal pain diarrhea uremia collapse unconsciousness mydriasis headache stiffness of neck, hemorrhages from stomach and lungs chrome holes on hands and mucous membranes of nasal septum and respiratory passages dermatitis	History	Gastric lavage and catharsis intravenous fluids with plasma infusion for shock if necessary Try dimercaptol (BAL) intramuscularly (p 767)
Dinitrophenol	Dinitrophenol workers dye workers explosives workers pharmaceutical workers shell fillers and wood preservers	Acute poisoning produces burning thirst nausea restlessness flushing sweating rapid breathing cyanosis fever and death with anoxia Chronic intoxication may produce peripheral neuritis anemia granulopenia purpura gastro intestinal irritation anorexia vom ting jaundice renal and hepat c in ufficiency cataract format on may occur aft r a long in t val	History	Symptomatic

rhythm due to hyperexcitable ectopic foci (p 862) Excitability is increased by *digitalis* which, when the heart muscle is already hypertonic, is capable of reproducing the entire range of the cardiac irregularities (ECG 72 74)

Origin and Spread of Wave of Excitation—The origin and spread of the wave of excitation in heart muscle are best followed through electrocardiographic studies The wave initiates in the *sino-auricular* (SA) *node* it spreads through the *auricular muscle* in all directions and with equal velocity The *auriculoventricular* (AV) *node* acts as a relay station it receives the impulse and transmits it to the ventricles by way of the *AV bundle* at the bifurcation, the waves spread simultaneously to the ventricles and reach the *myocardium* through the *Purkinje cells*

Contractility of the Heart—Cardiac excitation results in contractility a property which obeys two important physiological rules The first of these is the *all or none response* of the heart muscle by which each stimulus capable of causing contraction produces a maximum effect

The second rule of contractility relates to the existence of a refractory period which follows active contraction This is the interval in which the muscle will not respond to any stimulus *no matter how powerful* The *refractory* period is clinically manifest as the *compensatory pause* that follows a premature contraction (p 887) producing what the clinician recognizes as a *missed beat*

Digitalis probably increases contractility as a therapeutic effect

Rhythmicity—The rhythmicity of the heart is a function of specialized primitive muscle tissue the *sino-auricular node* (SA) of Keith and Flack The SA node or *pacemaker* is interspersed with nerve cells and fibers it is situated in the right auricle at the entrance of the superior vena cava it possesses its own blood supply and is set for an average beat of 72 to the minute though normal variations are of frequent occurrence in clinical practice

In addition to the normal cardiac pacemaker the heart possesses the *auriculoventricular* (AV) *node* of Aschoff Tawara This structure is situated in the interauricular septum and may assume the function of the pacemaker when the SA node has been destroyed or depressed When the AV node initiates the pace the clinical condition of *nodal rhythm* is observed (p 8 3)

The SA and AV nodes are not connected by special tissue their only means of contact is the auricular muscle

Conduction of the Cardiac Impulse—Nodal impulses are carried from the pacemaker to the chambers of the heart by the *auriculoventricular bundle of His* a well-defined grouping of muscular tissue The AV bundle passes from the AV node over the septal leaf of the tricuspid valve to the interventricular septum Here it divides into a *right and left branch* each passing to the corresponding chamber Its terminal arborizations the *cells of Purkinje* are histologically characteristic and differ visibly from the cells of the nodes and bundles they penetrate deeply into the ventricular muscles and are interspersed with nerve elements

Disturbances of conduction lead to *heart block* *Vagal stimulation* and *digitalis* impair conductivity and favor blocking the latter effect is valuable in auricular fibrillation (ECG 65) but it is a toxic manifestation in sinus rhythm (ECG 3)

Cardiac Circulation—The nutrition of heart muscle is dependent upon its blood supply through the *coronary vessels* and the *veins of Thebesius* Through these channels blood must be delivered, under a sufficient head of pressure to flow effectively through the coronary circulation

Coronary Arteries—Heart muscle is supplied by two coronary arteries the *left* divides into a circumflex branch and a larger anterior ramus descendens the *right* coronary artery terminates posteriorly in several descendin branches that go to the right ventricle special twigs *supply* the sino-auricular node and the conducting system

There are many variations in the distribution and anastomoses of the several branches accounting for the protean clinical manifestations of coronary artery disease Subsidiary systems of arterial *anastomoses are of the greatest importance in coronary occlusion* they determine the extent of the injury and the possibility of recovery Communications exist between the coronary branches themselves through ext acardiac branches of the aorta and by way of arterioluminal and arteriosinusoidal vessels which run from the coronary artery into the cavities of the heart There are almost limitless possibilities for auxiliary avenues to maintain myocardial nutrition when normal coronary trunks are blocked This principle underlies the surgical treatment of coronary thrombosis by the production of artificial *anastomoses* through pericardial adhesions

TABLE 50.—CLINICAL MANIFESTATIONS, DIAGNOSIS AND TREATMENT OF POISONING FROM NONGASEOUS TOXIC SUBSTANCES (*Continued*)

Substances	Occupations	Clinical Manifestations	Diagnostic Features	Treatment
Mercury		See p 765		BAL (p 767)
Metal Fumes	Zinc workers lead mercury manganese arsenic cadmium antimony processers	Dryness of throat hacking cough nausea and headache chills fever pain in extremities leukocytosis (metal fume fever)	History	Symptomatic
Methyl Alcohol	Denatured alcohol workers art glass workers artificial flower and leather workers painters paint makers paint removers bookbinders brush makers rubber cementers rubber workers dry cleaners dye makers explosives workers feather workers felt hat makers lamp filament makers furniture polishers safety glass makers ink makers lacquer makers and lacquerers linoleum makers lithographers methyl ester workers patent leather workers perfume makers photographers photoengravers metal polishers polish makers printers pyroxylin plastics workers rayon workers resin makers shellac makers shoe factory workers soap makers straw hat makers textile printers upholsterers vulcanizers wood alcohol distillers	Depression of central nervous system and heart delirium vomiting upper abdominal pain lacrimation photophobia respiratory tract irritation dyspnea cyanosis cardiac irregularity respiratory or circulatory failure visual disturbances with atrophy of optic nerves pupillary dilatation with loss of light reflex	History	Gastric lavage with 4 per cent sodium bicarbonate morphine if necessary intravenous plasma for shock lumbar puncture to relieve increased intracranial pressure artificial respiration where necessary Give intravenous drip of 1000 cc Ringer's solution containing 160 cc molar solution of sodium r lactate Supplement with oral bicarbonate Repeat for 4 or 5 days whenever pH of urine falls to 7 0
Naphtha	See Benzene			
Nickel	Alloy makers coin makers electroplaters enamelers nickel workers steel alloy makers storage battery workers	Edematous vesiculated exanthem with marked itching behind ears from eyeglass frame or wrist from watch on hand in industry	History	Symptomatic

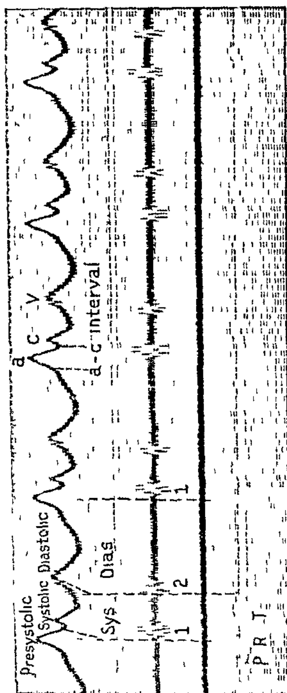


Fig 114 —Simultaneous records of venous pulse, heart sounds and electrocardiograph (Lead II) to demonstrate time relations Ordinates 0 04 and 0 2 second On the venous record the designation of *waves according* to two systems is indicated

From Wiggers Textbook of Physiology Lea and Febiger

TABLE 50.—CLINICAL MANIFESTATIONS, DIAGNOSIS AND TREATMENT OF POISONING FROM NONGASEOUS TOXIC SUBSTANCES (*Continued*)

Substances	Occupations	Clinical Manifestations	Diagnostic Features	Treatment
Radioactive Metals	Chemical and laboratory workers concerned with radium research, dentists, incandescent mantle makers, inspectors and examiners using fluoroscopic or x ray technic, radium paint, physicians, nurses and technicians who handle radium	Radium, *thorium* and uranium may produce local dermatitis, burns, malignancy, bone decalcification with pathologic fractures, osteogenic sarcoma, leukemia, anemia, leukopenia, sterility	History	Symptomatic
Selenium	Alloy makers, Portland cement makers, copper smelters, *glass workers*, lead smelters, lime burners, paint and pottery workers, pyrites burners, synthetic resin makers, selenium workers, steel alloy workers, sulfuric acid workers, vulcanizers, welders, zinc smelters	In selenium areas such as Nebraska and South Dakota, *gastro intestinal* disorders and hepatic insufficiency result from ingestion of selenium-containing meat, eggs, vegetables and milk; patients display also nervousness, garlic odor to breath, metallic taste, dermatitis, pallor and irritation of nose and throat	History	Symptomatic
Silver	Silver coin makers, indelible-ink makers, silver miners, mirror silverers, photographic film makers, silver polishers, *silver foil makers, silver processors of all types*, silver platers, [illegible]	Ingestion causes gastroenteritis and shock; chronic argyria results in greyish blue pigmentation of skin and mucous membranes	History	Symptomatic

occurs before sufficient blood has entered the cavity to guarantee an optimum cardiac out put. It is for this reason that slowing of the ventricular beat as is effected by digitalis in auricular fibrillation produces its remarkable therapeutic effect

See *QRS and T Changes* (pp 806 807)

The Heart Val s—The heart valves consist of pairs of auriculoventricular and arterial units

AV Valves—The AV valve is the *tricuspid* on the right and the *mitral* on the left the former has three and the latter two leaflets composed of double layers of endothelium strengthened by a few tissue fibers of connective tissue Each leaflet is attached, at *its base* to the fibrous ring that surrounds the auriculoventricular opening the free margins are connected to the papillary muscles by delicate *chordae tendinae* these prevent inve s on of the valves into the auricle during ventricular systole At the commencement of systole the chordae are held taut by the contract on of the papillary muscles

Durin auricular systole the leaflets occupy a m d posit on as the result of the forces of the two opposing currents with ventricular contractions the valves are swung closed by the n ng intraventricular pressure and just prior to valve closure the filling ventricle floats the leaflets upward due to eddy formation

With *stenosis* of AV valves protodiastol c or presystolic murmurs are heard *insufficiencies give rise to systolic murmurs*

Semilu ar or Arterial Valves—The sem lunar valves of the aorta and pulmonary ar teries form three small pockets which open toward the arterial lumen During the isometric phase of ventricular contraction AV an d semilunar val es are closed and intraventr cular pressure rap dly rises When the latter exceeds arterial diastolic pressure the aortic valves open and the ejection period begins At the termination of this phase centripetal currents in the arteries carry the valves into apposition and firm closure is again effected by the higher pressure within the arterial system

In contrast to the time relationships of defects of the AV valves *insufficienc es* of the semilunar valves are characterized by diastolic murmurs while *stenoses* produce systolic murmurs

H rt Sou ds and M m s—The heart sounds are graphically depicted by phonoca diography (p 801) at each area two sounds are heard d ff ring in quality duration and p tch

F rst Apical Sound—The first ap cal sound s produced by contraction of the ventricu lar muscle closure of AV valves and the vibrations of the alve leaflets and cho dae as traventr cular pressure rises Of these factors the closure of the AV valves is the most impo tant *Mitral nsuffici ncy murmu s* follow and *stenotic murmurs* precede the first apical sound the latter are as oc at d with accentuation of tl e first sound

Second Apical So nd—The second apical sound results f om vibrations set up in the blo d column and arterial walls as the aortic and pulmonary valves are placed under tension *following* their closure The second ap cal sound s muffled and may be inaudible in the p esence of a loud mitral stenotic mu mur

Basal Sounds—In early life when the pulmonary and aort c systems are relatively equal in importance the aortic second sound is no louder and often somewhat softer than the pulmonary second sound ($P_2 > A_2$) In the normal adult the aortic second sound exceeds the pulmonary *second sound* ($A_2 > P$)

The *insufficiency murmur especially heard in the aortic area (Fig 1030 p 3 0)* follows the second sound whereas the *stenot c murmur* is systolic With increase in the tension of the greater circulation the aort c second sound tends to become louder with increase n the pressure of the pulmonary circulation such as particularly occurs in mitral stenosis the pulmonary second sound is acc ntuated Diminution in the intensity of a prev ously accentuated second sound may suggest the onset of circulatory failure

Reg lat n of Cardiac Action—Cardiac behavior s regulated by neurogenic humoral and mechanical influences

The Nerves of the Heart—The nervous control of the heart includes *card o nh bito* and *accel ator* or *ugmentor mechanisms* the inhibitory act n occurs through the *cholin ergic vagi* accelerat on is a property of the *thoracolumbar* or *adrenerg c d v s on* (p 4) of the involuntary nervous system

THE VAGI—The vagus nerves are concerned with cardiac impulse production and con duction fibers from the *right vagus* terminate in the neighborhood of the *sino auricula node* and are essentially concerned with mpulse production The *left nerve* establishes a

TABLE 50—CLINICAL MANIFESTATIONS DIAGNOSIS AND TREATMENT OF POISONING FROM NONGASEOUS TOXIC SUBSTANCES (*Continued*)

Substances	Occupations	Clinical Manifestations	Diagnostic Features	Treatment
Thallium	Artificial gem making dye making depilatory making exterminating light bulb filament making sulfuric acid workers glass making insecticide workers thallium workers and thermometer makers termite and rat poison makers	Acute poisoning causes abdominal pain diarrhea vomiting hematemesis melena stomatitis peripheral neuritis cranial nerve palsies retrobulbar neuritis and respiratory failure Chronic poisoning results in hepatic and renal insufficiency loss of hearing loss of hair eosinophilia lymphocytosis and ocular disorders	History	Symptomatic
Trichlorethylene	Metal burnishers rubber workers disinfectant makers dry cleaners dye makers electroplaters oil and fat extractors galvanizers illuminating gas workers glue workers insecticides makers lacquerers lacquer makers leather workers painters paint removers perfume makers petroleum refiners pharmaceutical workers photographic workers polish makers resin makers shoe factory workers soap makers trichlorethylene workers varnish makers	Acute poisoning causes excitement nausea vomiting inebriation followed by somnolence and unconsciousness Vertigo anorexia headache and impaired cardiac action may appear later Chronic poisoning produces injury to optic and trigeminal nerves	History	Symptomatic
Toluol and Xylol	See Benzol			

relationship with the *auriculoventricular node* and is more important in the conduction mechanism In either instance stimulation of the nerve impairs cardiac efficiency by slowing the heart rate or blocking conduction

The vagus normally exerts a tonic action which is dependent upon afferent impulses that flow to the vagal center along the *carotid sinus* and the *aortic nerves* Excessive stimulation of the afferent fibers in the arch of the aorta or in the carotid sinus results in cardiac slowing and attacks of *vasovagal* or *carotid sinus syncope* (p 922) section or removal of these fibers increases heart rate

1 PHARMACOLOGY OF THE VAGUS—In the human subject, vagal effects may be produced by drugs Depression of the vagal mechanism by *atropine* or *belladonna* results in a more *rapid pulse rate* *vagal stimulation by physostigmine causes bradycardia* *Digitalis* possesses vagal activity that is most marked on the conducting mechanism the *heart block* produced in auricular fibrillation is of potent therapeutic efficacy

2 THERAPEUTIC VAGAL STIMULATION—Neurogenic mechanisms may be activated by reflex activity The vagus is stimulated by pressure upon the eyeballs (*oculocardiac reflex*) by compression of the carotid sinus in the neck by emesis or by the inhalation of an irritating vapor such as ammonia Each of these agencies is employed therapeutically in attempts to control *paroxysmal cardiac irregularities* (p 8/3)

3 UNTOWARD EFFECTS OF REFLEX VAGAL STIMULATION—Untoward effects of reflex vagal stimulation are observed in pugilistics when the victim is punched on the point of the chin or in the solar plexus In clinical medicine examples of harmful vagal stimulation arise from compression of the carotid sinus the eyeballs or the testicle the rough handling of abdominal viscera or pleural shock that occasionally results when the membrane is pierced by an exploring needle

See *Syncope* (p 922)

THE ACCELERATOR OR AUGMENTOR NERVES—The spinal cardio-accelerator centers are situated in the *lateral horns of the upper thoracic segments from the first to the fifth* thoracic vertebrae *Preganglionic adrenergic fibers* enter the ganglionated cord of the sympathetic to connect with cells in the inferior middle and superior cervical ganglia (p 1388) *postganglionic fibers* form the inferior middle and superior cardiac nerves

Stimulation of any portion of the accelerator mechanism causes an increase in pulse rate and an elevation of vascular tension This is best demonstrable pharmacodynamically by injections of epinephrine and associated amines injection of alcohol into the *stellate ganglion* produces some slowing of the heart rate and a transitory fall in blood pressure

RECIPROCAL INNERVATION—Cardio inhibitor and cardiac accelerator mechanisms are regulated by continuous discharges of impulses from all parts of the body The two systems act *reciprocally* and are *mutually restraining providing for the extraordinary adaptability* of the circulatory mechanism An *autonomic imbalance* is the physiological basis of the *cardiac neuroses* (p 89)

Reciprocal innervation is best illustrated by the relationship between blood pressure and pulse rate ordinarily a significant rise in arterial pressure is accompanied by slowing of the heart whereas a fall in tension produces tachycardia This compensatory mechanism probably initiates within the cardiac tissue or in the aortic arch where nerve fibers occasionally merge to form a recognizable *aortic* or *cardiac depressor nerve*

HUMORAL INFLUENCES ON CARDIAC INNERVATION—Cardiac neurogenic mechanisms may be affected by *humoral influences* Substances of the nature of *acetylcholine* and the *pressor amines* with an epinephrine-like action may conceivably be formed in the course of normal and disturbed tissue metabolism The isolation of pressor substances from kidney tissue (p 2273) has stimulated the search for antagonistic substances to be used in the treatment of *hypertension* (p 900)

SENSORY MECHANISM OF THE HEART—The normal heart does not respond with painful sensation when exposed to ordinary types of stimulation The surgeon who exposes the heart in the course of a technical procedure notes that manipulation and needling of pericardium and cardiac muscles cause no distress to the conscious patient

ANGINA PECTORIS—Despite the recognized tactile anesthesia of the heart circulatory abnormalities are capable of producing *angina pectoris* (p 890) which is one of the most painful sensations known to the human sufferer The investigations of physiologists promise to consolidate the seemingly divergent observations in all likelihood angina results from *anoxemia of the myocardium* the clinician confirms this possibility when he observes that *oxygen inhalations* relieve anginal pain while oxygen deprivation may produce angina in the afflicted

Lead

Sources —The accumulation of excessive amounts of lead in the body leading to *plumbism* results from the absorption of the metal from the gastro intestinal tract the respiratory epithelium or through the skin

Nonindustrial poisoning is usually due to ingestion In the home the metal enters the drinking water from lead pipes and lead lined water tanks Wine beer and cider made and stored in lead containing pottery may contain toxic amounts Breast fed infants become poisoned from lead nipple shields and from lead acetate ointment used as an astringent when the breasts are sore and irritated Slightly older children not infrequently gnaw lead paint from their toys and cribs (pica)

In industry the respiratory and cutaneous routes of absorption are more important than the oral although in many instances all three are involved Exposure to lead occurs in the following partial list of occupations lead mining smelting and refining handling and fabrication of metallic lead manufacturing lead salts and lead oxide manufacturing of storage batteries paints rubber compounding pottery dipping tree spraying linotyping and printing plumbing and gasoline manufacture

The addition of tetra ethyl lead to gasoline constitutes an important source of *skin penetration* leading to plumbism In industry the inhalation of lead fumes is the chief portal of entry and is the most important route leading to lead poisoning Lead that is inhaled is much more toxic than lead which is ingested

Behavior of Lead in the Body —On entering the body fluids lead is carried as a *soluble diphosphate* and is precipitated in the bones as the insoluble *tertiary lead phosphate*

The excretion of lead in a group of normal medical students amounted to 0 24 mg per day in feces and 0 04 mg per liter in urine The mean blood lead determined spectrographically was 0 06 mg per cent The mean urinary lead excretion of nine normal individuals determined over a period of three months ranged from 0 06 to 0 08 mg per liter or 0 05 to 0 1 mg in twenty four hours The source of this lead is the daily ingestion of food which contains 0 25 mg of the metal

When large quantities of lead are inhaled or absorbed excretion does not keep pace and *storage* occurs All forms of lead irrespective of the manner of absorption are distributed to the tissues in characteristic fashion Immediately after absorption the greatest amount of lead appears in the *spleen liver* and *kidneys* After a few days it collects entirely in the *bones* This lead causes no deleterious effects Hence the crux of the problem of treatment is that of controlling the deposition and excretion of osseous lead

The mechanisms of *lead deposition and excretion* depend on the metabolism of bone The direction of the lead stream is similar to that of the calcium stream The bony trabeculae act as readily available sources of calcium They supply or store calcium at a very rapid rate depending on the body needs Lead is stored in the trabeculae in high concentration

Not all the lead deposited in bone is excreted when it is liberated It is repeatedly dissolved and redeposited along the *epiphyseal lines* of growth especially in children

Any factor that favors the deposition of calcium in bone favors the

Just as the proof of the pudding is the eating so the cardiac output is the *final determinant* of the sum total of the effects of the factors which influence the physiology *of the circulatory system Since cardiac output is not directly measurable by methods that* can be employed in everyday practice *laboratory investigations* furnish incomplete and in adequate information unless interpreted in the light of clinical judgment Insistence on this viewpoint is necessitated by the current worship of blood pressure readings and electrocar diographic tracings to the exclusion of bedside observation

The Card ac Act on Current—The wave of contraction in the heart is due to or accompanied by a cardiac action current which is recorded by the *electrocardiograph* An atlas of electrocardiography is included (p 811) to illustrate the normal and pathologic variants disclosed by this valuable diagnostic adjuvant

THE DISTRIBUTING AND COLLECTING SYSTEMS OF THE CIRCULATION

The blood that is ejected from the ventricular chambers is distributed through the arteries and the arterioles to the capillaries from the capillary bed it is collected in the enules and returned through the larger veins to the cardiac auricles

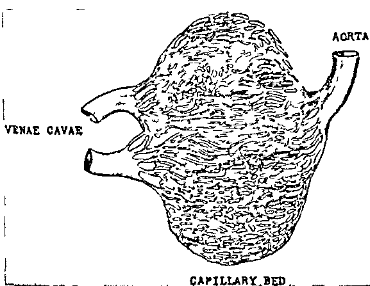


Fig 115—Diagrammat c representation of the expansion of the vascular bed in the capil lary area (capillary lake) *

H modynam cs—During each ventricular systole blood is ejected into the aorta under a measurable head of pressure A portion of the systolic thrust s utilized for the onward movement of the column of blood (*kinet c energy of flow*) The remainder distends the arterial wall increases the capacity of the vessel and is momentarily stored as *potential pressu e energy* Potential pressure energy is converted into kinetic energy during diastole thus insuring *a continuous flow through the cap llaries*

Aort c pressure reaches its maximum during mid-d astole and ts minimum at the end of diastole in the systemic vessels read ngs are made by means of the *sphygmomanometer* (p 3486) these prov de conside able informat on of valu n clini al med cine (pp 868 917)

Bl od V loc ty—Together w th the p essure changes in the vessels the e are varia tions in blood velocity The speed of bl d flow is greatest in the arteries it is reduced several hundred times in the capillaries it increases again upon return to the venous chan nels So striking is the pooling in the cap llary areas that the vascular bed may be regarded as a cap llary lake the reduct on n velocity permits of a more advanta eous nterchange of gases metabolites and waste products between circulat ng flu ds and fixed cells

* Best and Taylor Physiological *Basis of Medical Practice* W lliams *and Wilkins Com*pany

polychromatophilia Basophilic granules are probably derived from the basophilic substance of young corpuscles as a result of the action of lead

Basophilic stippling is not a specific sign of lead poisoning It occurs in pneumonia in infants leukemia pernicious anemia severe anemia due to neoplasms hemolytic anemia and aniline poisoning

Clinical Manifestations *Acute Lead Poisoning*—When lead salts are accidentally taken by mouth an acute episode results which differs from the manifestations of chronic lead intoxication *Nausea vomiting abdominal pain metallic taste* and *black stools* due to the formation of lead sulfide are the common symptoms Occasionally patients will develop *shock paresthesias oliguria* with *urinary abnormalities* and *hemolytic crises* If the sufferer escapes death the symptoms of chronic lead poisoning may supervene

Lead Encephalopathy—In children lead poisoning produces *headache lethargy vomiting coma convulsions* and *paralysis Fever* is usually present *Lead lines* are rarely seen A definite diagnosis cannot be made on the basis of the clinical findings Laboratory aids are needed These may reveal the suggestive blood findings previously described Radiographs show lead lines along the epiphyses The *spinal fluid* is usually under increased pressure and may contain 10 to 110 cells and a positive globulin reaction Scarification of the skin with sodium sulfide shows a lead deposit in 25 per cent of cases Spectrometry may reveal the presence of lead in the blood Increased amounts are found in urine which may also contain glucose

Diagnosis—The diagnosis of lead poisoning rests primarily on the history The telltale *lead line* occurs in the long bones of affected children (not adults) and may be seen readily on x ray For confirmation the *urinary and fecal lead content* may be determined Since the body can tolerate a certain amount of lead without developing evidences of poisoning the mere presence of lead in the excreta does not establish the diagnosis Toxic effects may be anticipated when fecal lead exceeds 1 1 mg per day and urinary lead concentration is greater than 0 15 mg per liter

Lead may also be estimated in the blood Values for lead are of significance only during and shortly after exposure In lead hazard industries the daily urinary output should not exceed 0 1 mg per liter Stool lead should be less than 0 6 mg per day

Prognosis—Prognosis depends upon the severity of poisoning and the degree of damage which has been done *Lead neuropathy* is inclined to be stubborn The *psychotic manifestations* may be fatal or may become chronic Only rarely do they disappear entirely and rapidly

Lead colic usually responds to treatment or disappears spontaneously within a few days *General debility constipation* and *anemia* may last for weeks or even months *Lead encephalopathy in children* is serious and has an appreciable mortality

Treatment *Acute Poisoning*—Acute lead intoxication due to the ingestion of lead salts requires rapid removal of the poison by *gastric lavage* and *catharsis* with magnesium sulfate Beyond this the patient is treated symptomatically but a trial of dimercaptol (BAL) injected intramuscularly may be worthy of consideration (p 767)

Chronic Poisoning—The treatment of chronic lead poisoning has as its

Particularly characteristic changes in the form of the pulse curve are seen in aortic steno is and aortic regurgitation The tracing of an *aortic stenosis* (Fig 116) is of the *plateau* type while that of *aortic regurgitation* is abrupt, corresponding to the *water hammer pulse*

Arterial Tension—The height of the normal blood pressure is determined by the influences of at least five tangible factors These include the systolic thrust of the heart the resistance exerted in the arterial bed the amount of the circulating blood in the arterial portion of the vascular tree the viscosity of the blood and the elasticity of the vessel wall The relationships that exist between these variables determine the height of the pressure curve

HUMAN BLOOD PRESSURE—Human blood pressure is recorded in the brachial artery by means of the sphygmomanometer (p 3486) *systolic and diastolic readings* are obtained the *pulse pressure* is calculated by subtracting the latter from the former

See *Blood Pressure Abnormalities of* (pp 868 917)

The Arterial Pressure Gradient—There is a gradual slope of arterial pressure from aorta to capillaries The decrease approximates 20 mm of mercury until the finer arteriol s

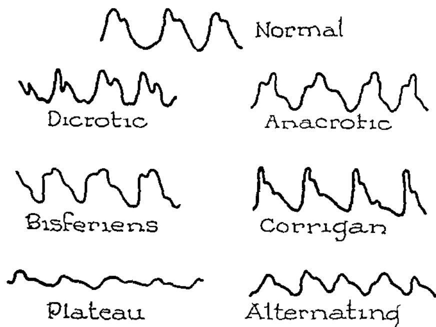


Fig 116.—Pulse tracings showing the various types of arterial pulse

are approached in these the pressure drops 50 to 60 mm of mercury due to the sudden increase in the surface area of the bed (Fig 117) Beyond the arterioles and capillaries pressure again rises gradually as blood returns to the larger collecting venous channels

THE VEINS—The anatomy and histology of the veins have received previous consideration (p 3578)

Greater Lesser and Portal Circulations—The architecture of the venous system is somewhat more complicated than that of the arterial portion In addition to the greater and lesser circulations respectively in the systemic and pulmonary regions there is a separate portal mechanism wherein splanchnic blood passes through two capillary systems the portal vein brings blood to the hepatic tissue from which it is again collected by the hepatic veins to enter the inferior vena cava The relationship of this system to liver disease is discussed in great detail with the material dealing with derangements of hepatic structure and function (p 1046)

Innervation—The veins like the arteries receive *constrictor* fibers from the adren

gam makers artificial flower makers thermometer makers mercury bulb makers manometer makers mercury boiler workers mercury bronzers mercury miners mercury salt workers mercury switch makers mercury smelters and solder workers mercury vapor lamp makers mirror silverers dry battery makers cap loaders cartridge makers cosmetics workers pottery decorators dental workers dentists detonator cleaners and fillers and packers dye makers, electroplaters embalmers and embalming fluid makers engravers explosives workers felt hat makers file makers fur handlers gold refiners hair workers incandescent lamp workers ink makers insecticide makers jewelers laboratory workers lead platers lithographers motion picture machine operators painters and paint makers pharmaceutical workers photographic workers physicians printers radio tube makers metal refiners storage battery makers tannery workers textile printers welders wood preservers and zinc electrode makers

Clinical Manifestations *Acute Poisoning*—The commonest form of acute poisoning by mercury follows the *ingestion of its bichloride salts* Many would be suicides might hesitate to use this method of ending their lives if they were forewarned of the suffering it entails First there is *severe pain in the mouth pharynx and upper abdomen* due to protein precipitation of the gastric and oral mucosa *Vomiting* at this stage helps to remove some of the poison Later the intestine is involved as evidenced by *bloody diarrhea* which may be severe enough to cause shock

The acute manifestations generally disappear as absorption proceeds only to be followed in a few hours by the more ominous systemic effects of the metal As mercury begins to be excreted in the mouth colon and kidneys severe *colitis* develops The transient initial polyuria is followed by *oliguria* and eventually *anuria* due to damage of the tubular system of the kidney Of all the sequels of the bichloride of mercury poisoning it is the renal effect which accounts for most fatalities

Severe *stomatitis* with foul breath and metallic taste usually develops one to two days after the poison has been ingested

Secondary to the disorders just described are profound disturbances in body fluids electrolyte and protein patterns *Dehydration* with diminished circulating fluid volume *acidosis shock* due to toxic capillary dilatation and *hypoproteinemia* all contribute to the lethal effectiveness of this substance

Chronic Poisoning—Prolonged exposure to mercury results from medication with its compounds or in manufacturing processes involving mercury

Clinical manifestations include stomatitis gingivitis excessive salivation a mercury line on the gums anorexia fetid breath and other gastrointestinal manifestations intention tremor exaggeration of the knee jerk scanning speech mercurial erethism loss of memory depression irritability anxiety insomnia and eczema In addition there is progressive renal impairment peripheral neuritis and anemia

Mercury may also produce the symptoms of metal fume fever (p 756)

Treatment *Acute Poisoning*—The treatment of early acute poisoning must be speedy to be effective since the prognosis depends on the time elapsing between ingestion and removal of the metal The patient should swallow *milk* or *raw egg* as convenient sources of protein to inactivate

THE "WHITE REACTION"—The skin manifests extraordinary responses to stimuli by mechanical and other agencies The simplest response is that of the "white reaction" which *follows gentle stroking* with a blunt instrument After a lapse of 15 to 20 seconds an area of pallor is seen along the path of stimulation the pallor attains maximum intensity in 30 to 60 seconds and then gradually fades to disappear in three to five minutes The white reaction is due to direct stimulation of the capillary wall

THE TRIPLE RESPONSE —A more complicated reaction is the triple response which consists of a red reaction a flare and a wheal The *red reaction* results from more firm pressure of the instrument it occurs after a shorter latent period of 3 to 15 seconds reaches its maximum in 30 to 60 minutes and gradually fades in a variable period The red reaction is due to capillary dilatation and is independent of nervous mechanisms

The *spreading flush* or *flare* results from an unusually strong or repeated stimulus the reddening of the skin surrounds the compressed area for a variable distance local temperature is elevated the flare reaction is due to arteriolar dilatation and it is dependent upon the *axon reflex* since it cannot be produced after the local nervous mechanisms have degenerated

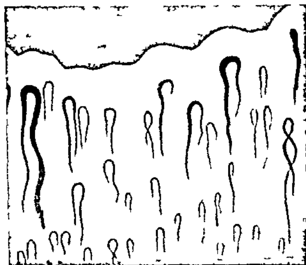


Fig 11 —The bed of the fingernail in a healthy subject, showing the capillary loops and the summits of the skin papillae The size of the structures is indicated by the 1/10 mm scale

THE WHEAL —A still more intense stimulus produces local edema or the wheal the skin area is elevated as in an *urticaria* (p 3345) there is transudation of fluid from minute vessels attesting to increased permeability of the capillary wall

Wheal production does not necessarily depend upon any neurogenic mechanism and is probably produced by *H substance* which resembles histamine it is liberated by the injured cells of the epidermis producing local chemical stimulation of the sensory endings of the skin and distant arteriolar dilatation through the mechanism of the axon reflex

The skin changes, in capillary loops have more than academic importance it is quite possible that similar occurrences involving wide areas of skin surface, may have tremendous significance in the conditions of *vasomotor collapse forward failure* (p 9 0) and *shock* (p 928)

The Lymphatics —The *lymphatic system serves as a collector of foreign* particles colloids and blood proteins that enter the tissue spaces In the case of bacteria, the lymphatics aid greatly in the body defense against infection (p 7o) Organisms are carried to the regional nodes where they are engulfed by *phagocytes in a successful resistance to infection*

After Lewis From Best and Taylor Physiological Basis of Medical Practice, Williams & Wilkins Co

CHAPTER 35

METHODS OF DIAGNOSIS OF DISTURBANCES OF THE CIRCULATORY SYSTEM, INCLUDING AN ATLAS OF ELECTROCARDIOGRAPHY

The routine methods used in diagnosis of circulatory phenomena appear with the material on the conduct of the physical examination (p 3548) The technics include inspection palpation percussion and auscultation of the precordial region examinations of the peripheral vessels and estimations of blood pressure

The more exacting tests involve determinations of circulatory time and venous pressures the two step exercise test the delineation of the cardiac contour by roentgenologic methods electrocardiography and electrophonocardiography

CIRCULATION TIME

The rate of blood flow is measured by determining the speed at which a readily detectable substance introduced at a fixed point in the blood stream reaches another fixed point in the circulatory system The circulation time for the *right circuit* is approximated by estimating the time that elapses between the injection of ether into the antecubital vein and the detection of its odor the circulation time of *right and left circuits* is measured by making an injection of saccharin decholin or calcium gluconate into the antecubital vein and recording the patient s subjective notation of a sweet taste a bitter taste or a sensation of warmth in the throat The taste time minus the ether time gives the approximate circulatory time for the *left circuit*

Ether Time —The ether time is determined in the following manner

1 The patient reclines in the dorsal recumbent position
2 The upper extremity into which the injection is to be made is supported throughout its length by a pillow placed in such fashion that the arm is 4 cm below the level of the sternum

3 A sphygmomanometer cuff is placed about the upper arm and inflated to 20 mm of mercury
4 The needle is introduced into the vein and the blood is drawn up into the syringe
5 The blood pressure cuff is deflated and the stopcock on the adapter is turned so that the blood may enter the manometer tube
6 When the blood column has ceased to rise the level is noted and this is reported as venous pressure
7 The normal venous pressure ranges between 4 and 9 mm of water Under abnormal conditions it may rise to 20 or 30 mm
8 After the reading has been made pressure is exerted in the right upper quadrant for a period of a minute
9 *The venous pressure reading is noted again a further increase indicates hepatic engorgement*

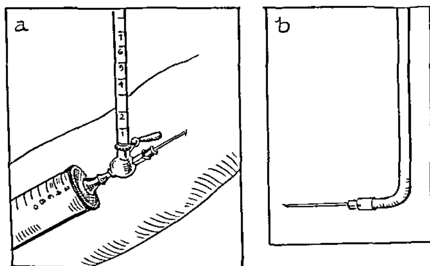


Fig 118—(*a*) The technic for direct determination of venous pressure using syringe and 3-way stopcock (*b*) L-tube also used in direct venous pressure determinations

THE TWO STEP EXERCISE TEST OF CARDIAC FUNCTION

The two step test of cardiac function is employed in the detection of the early *phases of coronary insufficiency* (p 895) *The test is of great*est value in patients who despite angina pectoris exhibit normal objective findings it should not be attempted in the presence of electrocardiographic changes

Technic —

1 The patient is weighed a blood pressure cuff is placed on one arm the *electrodes for the electrocardiogram are attached*
2 The patient reclines in a chair
3 The electrocardiogram is taken and serial blood pressure readings and pulse rates are recorded until they become stabilized

Sodeman in Pullen Medical Diagnosis

other through bridges of protoplasm which form a continuous nucleated sheath or syncytium This anatomic arrangement provides for complete integration of function See *Anatomic Review* (p 3545)

Living cardiac muscle possesses the inherent physiological properties of tonus, excitability contractility rhythmicity and conductivity

Cardiac Tonus—In physiological terms tonus is the optimum degree of slight contraction that exists when the muscle fiber is in diastole It is a condition of alert in which optimum relaxation is counterbalanced by optimum tension in order to provide for maximum response The sprinter who is on his mark is in a state of tonus his physiological status contrasts with that of the occupant of a hammock whose relaxation is too complete to provide a smooth and efficient response and differs also from that of the golfer who tightens up so that his swing is jerky poorly controlled and inefficient

Cardiac Hypotonus and Dilatation of the Heart—A stretching of the relaxed muscle fiber beyond its optimum causes a state of hypotonus In the heart hypotonicity is manifested by dilatation of the chambers increase of volume capacity and decrease in stroke output As a result there may be pooling of blood in the cardiac cavities and the production of *backward failure*

Changes in tonus are not depicted by clinical methods There is often a discrepancy between laboratory findings and the clinical observation of the condition of the patient, hence the records may be favorable but the appearance of the patient may not reflect the propitious reports

TABLE 51—VARIATIONS IN CARDIAC TONE

	Hypotonus	Isotonus	Hypertonus
Length of Fiber	Increased	Optimum	Decreased
Size of Chamber	Increased	Optimum	Decreased
Cardiac Volume Capacity	Increased	Optimum	Decreased
Volume Output	Decreased	Optimum	Decreased
Effect of Digitalis	Therapeutic	Toxic	Toxic

Cardiac Hypertonicity—Hypertonicity exists when in diastole the length of the cardiac fiber is less than optimum Under these circumstances the cavities of the heart have a lessened capacity volume intake is decreased systolic thrust is of less than optimum force and stroke output is diminished

Cardiac Hypotonus Hypertonus and Digitalization—Digitalis increases cardiac tonicity when the chambers are in a state of dilatation and the individual muscle fibers are increased in length beyond their optimum an increase in tonicity is a *favorable therapeutic effect*, when tonus is optimum or increased the effect of the drug is *harmful and toxic*. This physiological consideration warns the therapeutist to regard each digitalization as a clinical experiment

Beyond the absolute indications for digitalization the clinician is confronted with the problem of determining in each patient, when the prescribed digitalis has produced *its* optimum effect, for when the virtue has been overdone, the danger of toxicity is *imminent*. Rules of thumb for digitalis dosage (p 859) provide little assistance it is *only* by constant observation that it is possible to form a clinical judgment as to the *boundary* between therapeutics and toxicology

Excitability of the Heart.—The excitability of cardiac muscle is manifested by its ability to respond to stimuli Normally the pacemaker is the most sensitive area and it *initiates* the cycle of the heart beat When this structure is depressed or its sensitivity *is exceeded* by the sensitivity of other areas within the heart, the role of pacemaker may be *taken* up by an ectopic focus in this manner *cardiac irregularities* are produced

Effects of Quinidine and Digitalis—The property of excitability is diminished by *quinidine* (ECG 75 and 76) which acts favorably in the treatment of disturbances in *cardiac*

4 The patient performs the designated number of trips indicated in the table in the course of 90 seconds
5 *The patient resumes his seat in the chair and an electrocardiogram* is taken as rapidly as possible
6 Ninety seconds 105 seconds and 2 minutes after the completion of *the trips the blood pressure and pulse rates are taken*
7 The cardiogram blood pressures and pulse rates are recorded at two minute intervals for ten minutes

Interpretation—*Abnormalities include failure of blood pressure and* pulse rate to return to within 10 points of normal within 2 minutes depression of RST of more than 1 mm (0 1 mv) in any lead change of an upright T to a flat or inverted T *change of the T wave in the opposite direction* widening of QRS the appearance of bundle branch patterns or ectopic arrhythmias

See *ECG 14*, p *818 66*, p *843*

During exercise the T P interval may not return to the iso-electric level or the PR interval may become depressed without necessarily indicating coronary insufficiency

OSCILLOMETRY

The oscillometer permits a simple and objective evaluation of the state of arterial circulation in the limbs The instrument consists of a cuff similar to that used for the sphygmomanometer and dials which record blood pressure and vessel oscillations

The cuff is placed about the limb and inflated to a point well above the systolic level The pressure is then gradually released and the oscillations observed on the dial provided for the purpose As the pressure gradually diminishes the oscillations first increase in size and then gradually diminish The reading is taken at the point where oscillations are greatest

The *absence of oscillation* or the presence of *deflections* as small as 1 or 2 mm suggests marked arterial impairment Though the test is far from accurate it provides a simple and objective check on palpation particularly in the lower extremities where pulses are sometimes most difficult to feel even when patent

TESTS OF PERIPHERAL CIRCULATION

The simpler tests of peripheral circulation have been described (p 791) The status of the peripheral circulation may also be surmised from readings of *skin temperature* which require sensitive thermometers

At times it is necessary to determine the importance of *functional angiospasm* in peripheral arterial insufficiency Since the arterial tonus is controlled by impulses from the sympathetic nervous system vascular spasm can be eliminated by blocking the nerves carrying these impulses If the skin temperature rises markedly after peripheral nerve block the arterial deficiency is probably on a functional rather than an organic basis In the presence of organic occlusive arterial disease nerve block has little effect on skin temperature or oscillometry

A simpler but fairly effective method of testing for the presence of spasm is by the use of *alcohol* administered in the form of a good drink of

Coronary Veins—The collecting system of the heart consists of an extensive network of capillaries draining into larger veins and then into the cavity of the right heart. The recognized channels are the large and the smaller accessory *coronary veins* the *Thebesian veins* open directly into the cavities of the heart

Coronary Pressure Relationships—In general the pressure values in the coronary arteries resemble those of the carotids at the peripheral end of the anterior coronary vessels the general arterial pressure roughly corresponds to one fifth of aortic pressure

The maintenance of coronary pressure is of importance in the determination of the fate of the infarcted myocardial area in coronary occlusion With acute thrombosis and its accompanying shock the local musculature suffers from the combined effect of mechanical blockage of the nutrient vessel and diminution in the head of pressure

See *Coronary Insufficiency* (p 895)

Coronary Blood Flow—Coronary blood flow can be measured in animals experimental studies suggest that the volume flow in the human coronaries approximates 150 to 225 cc.

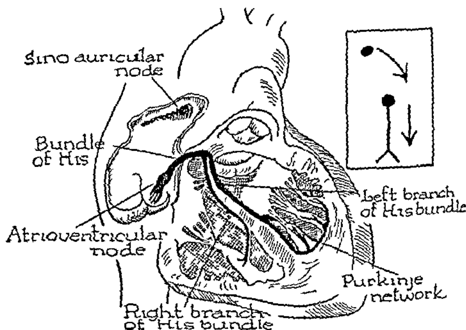


Fig 113—The specialized conduction system of the heart Inserted is a diagram of the conduction system representing the normal spread of the impulse This diagram and variations of it is used in the illustrations of the cardiac irregularities to follow to indicate normal and disturbed conduction

per minute About 75 per cent of the blood flows through the left artery and only 25 per cent through the right coronary branch

The factors that may possibly control coronary flow include (1) The *head of pressure in the aorta* (2) *the mechanical massage that occurs when the caliber of* the coronary vessels is altered through ventricular systole and diastole and (3) changes due *to reflex vasomotor action* The relative *importance of each of these factors and* their mechanisms remain as yet, obscure and controversial However their recognition emphasizes the possibility that *coronary insufficiency may arise as the result of* remediable functional alterations in hemodynamics and innervation (ECG 11 12 13 and 14)

See *Coronary Occlusion* (p 983) *Coronary Insufficiency* (p 895) *Angina Pectoris* (p 890)

Chemical Control of the Heart—The chemistry of heart muscle involves the effects of known nutritive and pharmacodynamic substances as well as unknowns whose nature and *importance* remain as yet to be elucidated

* Sodeman, in Pullen Medical Diagnosis

RIGHT ANTERIOR OBLIQUE VIEW—In the right anterior oblique view the right shoulder of the patient is placed against the screen *Anteriorly* the heart border is formed from below up by the right ventricle the pulmonary artery and the ascending aorta

The *posterior* border of the heart is made up from above down by the left auricle the right auricle and the inferior vena cava

The trachea and right bronchus are observed as areas of lesser density between the upper descending aorta and the posterior cardiac wall The esophagus lies between the descending aorta and the heart Its course may be visualized by giving the patient a thick barium mixture to swallow Normally there are small indentations in the barium column from the aorta the right bronchus and further down where the esophagus passes through the diaphragm

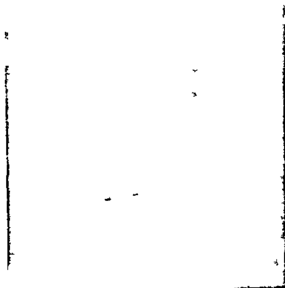


Fig 120—Cardiac silhouette of normal male 44 years of age Right anterior oblique view

The inferior border of the right anterior oblique aspect of the heart is formed from left to right by the inferior vena cava the right auricle and the right ventricle

THE LEFT ANTERIOR OBLIQUE VIEW—In the left anterior oblique position the left shoulder of the patient is placed against the screen From above down are seen the *ascending aorta* the *right auricular appendage* and *right ventricle* The right ventricle is difficult to differentiate from the appendage which lies above it The appendage has a diagonal border whereas the anterior edge of the ventricle is almost vertical The ascending aorta merges into the arch and thence into the descending portion The arch can often be visualized by cutting down the screen diaphragm Within the arch is the bifurcation of the trachea

The definitive metabolic substances are oxygen and carbon dioxide calcium sodium, potassium, glycogen and dextrose Pharmacodynamic elements may include chemicals related to acetylcholine and epinephrine additionally products derived from the kidneys may be of significance under pathologic conditions

See *Angiotonins* (p 901)

Oxygen and CO Tensions—Cardiac muscle is capable of contraction only when it has an adequate oxygen supply With anoxemia or hypercapnia there develops a myocardial insufficiency (p 890) which may be functional and transitory or organic and of longer duration anoxia is particularly related to *angina pectoris*

Hydrogen Ion Concentration (pH)—Heart muscle is highly sensitive to changes in hydrogen ion concentration and has a low buffering power circulatory failure may be anticipated in conditions of alkalosis and acidosis (ECG 44 and 48)

Calcium Rigor and Potassium Inhibition—The calcium and potassium salts of the perfusate sensitively alter cardiac function under experimental conditions *Excess of calcium* produces calcium rigor in which the heart beat ceases in the fully contracted state much as in *digitalis poisoning* The action of *excessive potassium* is opposite to the calcium effect, an absolute increase of potassium or a relative diminution in calcium causes the heart to come to rest in a state of relaxation potassium inhibition resembles *cardiac dilatation*

The calcium potassium effects are theoretically but not practically important calcium-potassium balance is so nicely adjusted (p 602) that the administration of either salt has little or no appreciable effect on the blood ratio In our opinion therapeutic doses of calcium or potassium do not strengthen cardiac contraction nor enhance digitalis effects

The Cardiac Cycle—The cardiac cycle consists of auricular systole and diastole and ventricular systole and diastole these periods are best described by noting the pressure changes that occur within the auricles and ventricles

Intra auricular Pressure—The intra auricular pressure curve has three crests the first positive or *a* wave is due to auricular systole corresponding to the contraction of the muscle fibers in the auricles the *a* wave is followed by a small *c* wave due to the rising pressure in the ventricle as this chamber commences its contraction this pressure is transmitted to the auricle through the closed AV valves which bulge into the upper chamber The final positive *v* wave reflects the stasis resulting from the inflow of blood from the veins and its accumulation in the auricle while the AV valves are closed

AURICULAR SYSTOLE—The auricular contraction is obviously of relatively minor importance this is best illustrated in auricular fibrillation which is often compatible with normal circulatory dynamics despite the absence of any propulsive force from the upper chamber

See *P Wave Changes* (p 806)

Intraventricular Pressure—The intraventricular pressure curve runs parallel to the intra auricular curve for long stretches in the cardiac cycle There is a small *positive wave* in the intraventricular curve that corresponds with the *a* wave in the intra auricular curve this is due obviously to the transmitted effect of the auricular systole At the termination of the *a* wave and between the auricular *a* and *c* waves ventricular systole produces a sharp rise in intraventricular pressure Since both the AV and aortic valves are closed intraventricular pressure rapidly mounts until it exceeds aortic or pulmonary diastolic pressure At this time the semilunar valves are forced open When intra arterial pressure exceeds intraventricular pressure the arterial valves close intraventricular pressure falls and diastole is initiated Finally when intraventricular pressure falls below intra auricular pressure, the AV valves open and blood is again received from the upper chamber

Ventricular Systole and Diastole—There are several clearly defined phases of ventricular systole and diastole In the former there is an *isometric period* which precedes the appearance of the arterial pulse in this period the muscle fibers are not shortened or contracted The isometric phase is followed by an *ejection period* during which the blood is discharged into the arteries as the fibers shorten and contract. The third or *isometric relaxation phase* is that in which the cavity of the ventricle is again closed the fibers having undergone relaxation and returned to their normal length

In diastole there is an initial *protodiastolic* phase followed by periods of rapid and then slower *filling* the auricular systole is reflected by a small pressure wave in the ventricular curve after which there is an inflow phase due to the discharge of blood from the auricular into the ventricular cavity

When the heart beat is excessively rapid the filling phases are curtailed, contraction

Posteriorly the uppermost portion of the silhouette is the left auricle and below is the corresponding ventricle the auriculoventricular groove separating the two chambers

The Cardiac Chambers Viewed Fluoroscopically—The fluoroscopic findings permit recognition of cardiac enlargement generalized or limited to one chamber abnormal pulsations and the relative strength of systole

RIGHT VENTRICLE—Enlargement of the right ventricle is seen earliest in the *right oblique position* as a bulge into the anterior mediastinum caused by enlargement of the outflow tract Later in the *postero anterior*



Fig 123—Cardiac silhouette postero-anterior view Patient with inter auricular septal defect The heart is markedly enlarged to the left, the pulmonary artery segment is prominent and the right pulmonary artery is hugely dilated and of increased density The barium filled esophagus was not displaced posteriorly The prominence of the pulmonary artery segment is due partially to marked enlargement of the right ventricle and partially to actual dilatation Note the prominence to the left of the left ventricle This is due mostly to displacement by the right ventricle

position there is straightening of the left cardiac border below the aortic knob associated with elongation of the pulmonary artery

Enlargement of the inflow tract (tricuspid valve to apex) follows that of the outflow tract It is signified fluoroscopically by a bulge in the lower portion of the *anterior border* best seen in the *left anterior oblique view* In addition the right ventricle occupies more space on the diaphragm causing an increase in the diaphragmatic projection of the heart

In the *postero anterior view* marked enlargement of the right ventricle causes a spread to the left rotating the left ventricle posteriorly

LEFT VENTRICLE—As in the right ventricle left ventricular enlargement begins with the outflow tract (apex to aortic valve) Fluoro

DIFFERENTIAL DIAGNOSIS OF

Alterations in Normal Cardiac Sounds

The normal cardiac sounds may be universally accentuated or diminished. Disturbances, which preponderantly involve systemic or pulmonary circuits may give rise to isolated accentuations or diminutions in intensity These have particular diagnostic importance Problems relative to abnormal sounds particularly murmurs are later discussed (p 97[illegible])

FINDING	CAUSES AND DIAGNOSTIC FEATURES
Accentuation of all sounds	Associated with fever excitement, exercise or the injection of adrenergens (epinephrine) In the linear chest With hypertension, hyperthyroidism and neurocirculatory asthenia Marked accentuation may be associated with pseudostenotic murmur at apex. Get blood pressure readings and B M.R.
Diminution of all sounds	With obesity pendulous breasts and emphysema Associated finding in bronchial asthma adhesive pericarditis pericardial effusion hemopericardium neoplasm of pericardium cardiac tamponade coronary occlusion, myomalacia and backward or forward failure Get x ray of chest and Ecg Prepare for pericardial puncture if indicated.
Accentuation of first sound at apex (often with reduplication)	With increased tension in auricle as result of hypertension of greater circuit, hyperthyroidism or mitral stenosis Valve defect associated with presystolic murmur and right axis deviation (p 970) Elevation of B M.R. in hyperthyroidism (p 1206)
Accentuation of second sound in second or third right interspace (often with reduplication)	With hypertension of greater circulation, syphilitic aortitis aortic aneurysm or glomerulonephritis Get chest x ray Ecg serologic test for syphilis urine and renal function tests
Accentuation in second or third left interspaces (occasionally with reduplication)	In youth With hypertension of lesser circulation, often in association with mitral stenosis (p 970) With lobar pneumonia and pulmonary tuberculosis particularly of the fibrotic variety Get chest x ray and Ecg
Diminution of apical first sound	With mitral stenosis Often associated with loud protodiastolic murmur right axis deviation and change in cardiac silhouette (p 797) Progressive lessening of sound in typhoid fever forward failure and coronary occlusion.
Diminution of second sound in second or third right interspace	With failure of greater circulation aortic insufficiency aortic stenosis or mitral stenosis. Cardiac murmurs with valvular defects. Get chest x ray for cardiac silhouette and Ecg for axis deviation (p 809)
Diminution of second sound in second or third left interspace	With pulmonary regurgitation or stenosis and tricuspid insufficiency Note murmurs (p 973) Get chest x ray for cardiac silhouette and Ecg for axis deviation (p 809)

of the heart Enlargement therefore proceeds early into the retrocardiac space If a patient with left auricular enlargement is given a thick barium paste to swallow while in the *right anterior oblique position* the lower portion of the esophagus will show backward displacement due to encroachment of the auricle into the space between the heart and the vertebral column When the patient is viewed in the *postero anterior position* the barium column shows a curve convex to the right As the auricle enlarges upward it can be seen in the *left oblique view* to obliterate the angle formed by the bifurcation of the trachea Further extension causes an upward pressure on the left main bronchus with a widening of the bifurcation angle and eventually an upward shift of the bronchus Occasionally



Fig 125—Cardiac silhouette postero anterior view Male 48 years of age with aneurysm of left ventricle after myocardial infarction at age of 44 Progressive cardiac enlargement to left Fluoroscopy reveals paradoxical pulsations of lower two-thirds of left border (ventricle expands during systole)

the left auricle enlarges to such an extent that it appears on the right heart border as visualized in the *postero-anterior view*

RIGHT AURICLE—The right auricle lies on the right posterior surface of the heart while its appendage pushes anteriorly and to the right In the *postero anterior view* this structure forms the lower right border of the heart Enlargement begins with the appendage and is evidenced fluoroscopically by lengthening of the horizontal component of the right cardiac border as seen in the left oblique position When the auricle itself enlarges the retrocardiac space just above the diaphragm is encroached upon but the shadow of the barium filled esophagus is superimposed upon it rather than deflected since this chamber lies to the right of the esophagus

The pathway by which anginal pain is transmitted is of practical importance in surgical attempts to relieve this painful condition the sensation travels through the sympathetic afferents to reach the central nervous system *alcohol injections* which block the ganglia are often effective therapeutic procedures (p 853)

MECHANICS OF THE HEART —There is no more remarkable mechanical device than the human heart this relatively small pump beats on the average of 72 times to the minute and 100 000 strokes daily In the course of the year the total pulse beats reach the astounding figure of 36 000 000 and the patient who survives to his allotted three score and ten, has approximated 2 500 000 000 individual cardiac beats without intermission repair or replacement of parts The mechanical principles which underlie cardiac activity are briefly summarized

1 THE LAW OF THE HEART —The law of the heart (Starling) enunciates the tenet that the energy set free at each contraction is a simple function of the fibers that compose its muscle wall The integration of function is established anatomically by the syncytial arrangement (p 772) physiologically it is assured by the orderliness of impulse production and conduction (p 773)

2 INITIAL AND DEVELOPED TENSIONS —Optimum contraction requires that the cardiac muscle fiber be increased to optimum length in the period of diastole Under such circumstances, it develops an optimum *initial tension* after which it contracts isometrically In its contraction or systole the *developed tension* increases up to a certain point with each increment in the initial length of the individual fiber beyond the optimum developed tension becomes lessened with increasing initial length until there is cardiac dilatation (p 870)

3 THE NORMAL OR OPTIMUM MECHANICAL CONDITIONS —The power of cardiac contraction is dependent upon initial length initial tension and developed tension in the individual fiber When circumstances are normal the initial length of the cardiac muscle fiber is optimum diastolic volume is optimum cardiac contraction is optimum and volume output is optimum

4 DEVIATIONS FROM THE NORM —Deviations from ideal mechanical circumstances are compensated by the enormous capacity of the heart to adjust itself to untoward conditions However there are limits to the mechanical perfection of this extraordinary pump with an *excessive diastolic increase* in the length of the fiber (dilatation of the heart) the contraction is feebler volume output falls and backward circulatory failure is imminent, with *lessened diastolic increase* in the length of the fiber as produced by digitalis poisoning the capacity of the cardiac chamber is decreased the contraction is less than optimum and circulatory efficiency becomes impaired

It is the task of the clinician to ascertain the optimum adjustment for this he is dependent upon clinical observation clinical experience and clinical judgment At the present time laboratory methods of investigation afford little help in the elucidation of many fundamental physiological problems Recognition of this fact liberates the practitioner from a slavish devotion to instrumental methods it encourages a return to dependence upon bedside observation in the management of the circulatory disturbances exhibited by the individual patient

Cardiac Output —The average heart weighs 300 gm it ejects 120 to 140 cc with each ventricular beat, the cardiac output per beat is the systolic discharge or *stroke volume* the output per minute (*minute volume*) is determined by multiplying stroke volume of *one ventricle* by pulse rate Thus the average heart which beats 72 times to the minute has a minute volume that approximates 6 to 9 liters or 3000 to 4500 cc for each chamber A more accurate estimation based on surface area gives a *cardiac index of 2 2 liters per* square meter per minute

Cardiac output may be markedly increased by physiological variants thus *exercise* is capable of stepping up the minute volume from 19 to 37 liters *elevation of temperature* beyond 36 C, sends up the output from 5 to 30 per cent *digestion* causes an increase of 30 to 40 per cent which accounts for the frequency of postprandial angina pectoris *pregnancy* may produce an elevation of 45 to 85 per cent in the late months of gestation *emotion* may cause changes of even greater magnitude

The heart increases its minute output by increasing stroke volume or minute rate The responses however may be overdone excessive rapidity of the heart, without adequate diastolic filling results in lowered minute output excessive cardiac filling produces a stretching of the muscle fiber beyond its optimum and an ineffectual contraction which is not compensated by increase of the minute rate

Aneurysm of the aorta is recognized as a localized usually sharply defined mass which can in no view be separated from the aortic shadow Pulsations may be absent transmitted or expansile Not infrequently small curved linear calcific deposits can be seen in the contours of the aneurysm

Aneurysm of the ascending aorta usually projects into the right lung field while ascending and transverse aneurysms cause displacement and narrowing of the trachea and bronchi Aneurysms of the arch produce widening of the upper mediastinal shadow and the esophagus and trachea are compressed and displaced backward and to the right In the descending

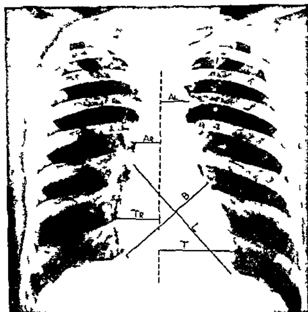


Fig 128—Teleoroentgenogram Transverse diameter = TR + TL Long diameter (L) extends from junction of cardiac silhouette and vascular pedicle on right to apex on left Broad diameter (B) is the greatest cardiac diameter perpendicular to L Aortic arch diameter = AR + AL

aorta the aneurysms may project beyond the right heart border or extend into the left lung field At times aneurysms can be large enough to occupy almost a whole hemithorax Change in contour or density of an aneurysm over a period of days or weeks suggests the possibility of a dissecting process

Dilatation of the main pulmonary trunk appears in the postero anterior position as a bulge below the aortic knob having the same convexity as the knob Acute pulmonary vascular stasis causes mottling and decreased radiability of the entire lung field This is often associated with increase in the size of the hilar shadow (Fig 124)

Courtesy of Picker X Ray Corp and Equitable Life Assurance Society

Circulation Time—In the clinic blood velocity is determined by measurements of the circulation time (p 787) The detection of the odor of *ether* on the breath after intravenous injection gives a rough estimate of the status of the right circuit the subjective taste of *saccharin* or *decholin* after intravenous injection approximates a completed round trip through both chambers

The Arteries—The arteries constitute a *high pressure system* that is separated by the arterioles and the capillaries from the venous or *low pressure system* The anatomy and histology of the arteries are elsewhere described (p 35"6)

The Greater Circulation—The blood that is ejected from the left ventricle passes through the aorta to the systemic arterioles and capillaries where it becomes progressively less oxygenated and more heavily laden with carbon dioxide this blood is returned by the systemic veins to the right auricle where its content of oxygen is minimum and its per centage of carbon dioxide is maximum

The Lesser Circulation—In contrast to the conditions that prevail in the greater circu lation the blood that is ejected from the right ventricle contains minimum amounts of oxygen and maximum amounts of carbon dioxide It is propelled through the pulmonary artery to be oxygenated in the pulmonary capillaries it is returned by the pulmonary veins to the left auricle

Under normal conditions the mean arterial pressure in the pulmonary circuit approxi mates a sixth of aortic pressure and measures in the vicinity of 20 mm in the human sub ject the pulmonary diastolic pressure is probably less than 10 mm

During inspiration the lungs hold approximately 9 per cent of total blood volume 6 per cent remains during expiration but the total quantity may be increased up to 20 per cent The distensibility of the pulmonary vascular bed encourages the insidious development of *hypostasis* and the early presence of *pulmonary edema* in backward failure

The Vasomotor Nerves—As in the case of the heart the arterioles have reciprocally antagonistic innervation from the sub-divisions of the involuntary nervous system the *ad renergic fibers* are *vasoconstrictor* while the less powerful influences of the *cholinergic repre sentations* are *vasodilator* The term *vasomotor nerves* is used to include vasoconstrictors and vasodilators

The Vasomotor Center—Both vasoconstrictor and vasodilator centers are present in the floor of the fourth ventricle of the medulla the vasoconstrictor area occupies the apex of the *ala cinerea* while the vasodilator center is just lateral to the *obex* Each center has bi lateral representations and is connected with areas in the *cerebral cortices* and the *hypo thalamus*

The vasoconstrictor and vasodilator centers are in tonic activity though the dilator element exists to minimum degree The tonic activity of the centers is dependent upon afferent nerve impulses received from organs and tissues of the body from other nerve centers in the cerebral cortex and the medulla and from changes in the chemical composi tion of the blood

Alterations in tonus may be effected by a variety of factors stimulation of the central end of the sciatic and other nerves may cause a rise or fall in arterial blood pressure the application of warmth produces vasodilatation pain and cold cause vasoconstriction vaso vagal reflexes may have such profound influence as to result in syncope (p 921) the aortic or cardiac depres or nerves stimulated by hypertension in the great vessels effect a fall in pressure due to splanchnic dilatation

Besides the sensitivity of the vasomotor centers to neurogenic stimulation these struc tures react to chemical influences vasoconstriction and hypertension result from high ten sions of carbon dioxide low oxygen tensions an increased hydrogen ion concentration medullary asphyxia as in increased intracranial pressure or an excess of circulating adren ergic substances Vasodilatation and fall of blood pressure or accompany carbon dioxide de pletion and increase in the concentrations of cholinergins such as acetylcholine

The Arterial Pulse—The arterial pulse wave may be visualized by the use of the sphygmograph which is applied to the radial artery The tracings so obtained have no longer much significance in clinical medicine In general they correspond to the pressure changes of the intraventricular curves there is an initial abrupt vertical upstroke (the *anacrotic limb*) and a more gradually sloping downstroke or *catacrotic limb* which has a dicrotic notch and a dicrotic wave

The anacrotic limb and the catacrotic limb up to its incisure represent systole of the ventricles the incisure corresponds to the closure of the aortic valves the remainder of the catacrotic limb is in ventricular diastole

Teleoroentgenography—The teleoroentgenogram is a chest film taken at a distance of five or six feet From it can be measured with great exactitude the diameters of the heart great vessels and thoracic cage Under normal adult circumstances the great vessels measure between 4 and 6 cm the right border of the heart is rarely beyond 4 cm from the mid sternal line and the left border except under pathological conditions does not measure more than 10 cm beyond the midsternal line The total diameter of the heart is thus less than 14 cm in a thoracic cage whose diameter is ordinarily in excess of 30 cm The ratio between total cardiac diameter and intrathoracic diameter is less than 1 to 2

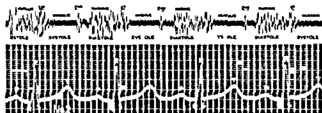


Fig 130—Mitral stenosis Stethogram at apex electrocardiogram Lead II Boy 8 years of age Chorea at 4 years and again at 6 years Probably low grade rheumatic fever since 6 years Rheumatic heart disease known since 5 years Hospital examination showed moderate systolic and moderate crescendic diastolic murmur Latter accompanied by a thrill The stethogram shows both murmurs clearly



Fig 131—Decrescendo diastolic murmur Stethogram at left sternal border electrocardiogram Lead II Boy 16 years of age Rheumatic fever dates from 11 years Two attacks since then last beginning at 15 years Rheumatic heart disease known since 1? years Auricular fibrillation of unknown duration (several months at least) Hospital diagnosis showed systolic murmur beginning immediately after first sound long flowing diastolic murmur beginning promptly after second sound A marked thrill accompanies the diastolic murmur Note especially the easily recognizable decrescendic murmur shown by the gradually decreasing height of the deflections, and the recording of the low pitch thrill by the wide spacing of the adjacent peaks of the diastolic murmur *

Angiography—Delineation of the lumen of vessels or the chambers of the heart through an intravenous injection of a radiopaque solution is an experimental measure whose practice is limited to experts It is of occasional value in the exact delineation of the type of congenital lesion in differentiating an aneurysm from a mediastinal neoplasm and in estimation of the extent of peripheral vascular occlusion

PHONOCARDIOGRAPHY

Mechanical methods of recording the heart sounds constitute a refinement in physical diagnosis Many of the modern electrocardiographic ma

* Courtesy of Sanborn Company

ergic system the constrictor mechanism is under tonic influences the *vasodilator mechanism* is less powerful but is demonstrably active with reduction in carbon dioxide tension

The Venous Pulse—The venous pulse is best visualized by observation of the jugular veins the waves correspond more or less to those of the intra auricular pressure graph (p. 770) They consist of an ascending *a* wave due to auricular systole an ascending c wave as the result of ventricular contraction with bulging of the AV valves into the auricle, the ascending *v* wave is due to filling of the auricle and the descending limb of the *v* wave results when the AV valves open and the auricle is emptied into the ventricle

Recording of the jugular pulse by the polygraph which also depicts the carotid waves, no longer furnishes information of sufficient value to warrant the performance of the test.

Venous Pressure—Measurements of venous pressure are obtained with great accuracy Ordinarily the readings vary between 4 and 9 cm of blood elevations to 20 or 30 cm are recorded in *right heart failure* (p 942) and in venous occlusions Of particular importance are the alterations in venous pressure that accompany pressure in the right upper quadrant when there is chronic engorgement of the liver

See *Backward Failure* (p 941)

The Capillaries.—The capillary beds consist of the endothelial lined vasculature that lies between the arterioles and the venules Each capillary has an average diameter slightly in excess of the diameter of an erythrocyte The sum of the sectional areas of these fine subdivisions of the vascular system is from 600 to 800 times greater than the cross section of the aorta These purely mechanical calculations are of tremendous significance in reference to blood flow blood velocity and blood pressure the increase of frictional resistance results in marked diminutions in blood flow and blood velocity and further reduction in blood pressure beyond that which occurs in the arterioles The *capillary lake* provides adequate opportunity for osmotic activity between circulating fluid and tissue juices

The Regulation of the Capillary Circulation—The capillary circulation is endowed with the capacity for independent regulation changes in capillary diameter are obviously not the result of neuromuscular activity since muscle fibers are not demonstrable in the cap llary wall The endothelial cells themselves are capable of contractility and seem responsible for the alterations in capillary diameters

H Substance—The mechanisms responsible for alterations of the capillary wall are difficult of accurate definition Efferent and afferent fibers are clearly demonstrable in the vicinity of capillaries Currently it is believed that capillary dilatation is brought about through humoral and neurogenic activity injured cells liberate an *H substance* which closely resembles histamine and liberation of this product produces a vasod latation through d rect action Additionally an indirect effect is accomplished through the medium of *axon reflexes* so that the changes in capillary diameter are shared by vessels in the surrounding area

The concept of the H substance is important in an appreciation of tl e mecl anism of *inflammation* (p 16) the product is capable of producing the card nal inflamm tory signs of redness heat swelling and pain

Capillary Pressures—Capillary pressures have been measured and appear to approximate 32 mm Hg in the *arterial limb* of the loop and 12 mm Hg in the *venous limb*

Capillary Pulsation—Capillary pulsation consists in rhythmical flushing alternating with pallor these changes correspond to heart beats The phenomenon is best observed in *aortic regurgitation* (p 9‾0) and *arteriovenous aneurysms*

Capillary Loops of the Human Skin—In the human skin, capillary loops are visualized by placing a drop of cedar oil at the base of the fingernail and making observations under the low power of the microscope Here it is seen that the *proximal* or *arterial l mbs* ascend in the papilla and make a hairpin turn to form the *venous limb* which runs into the *subcapillary venous plexus* The latter presents a large surface area that is parallel to the skin and determines for the most part the alterations in skin color and temperature

SKIN COLOR—An intense *scarlet color* of the skin indicates normal or increased blood flow in dilated vessels the *deep blue color of cyanosis* accompanies a slow blood flow with dilated vessels *light pink* is seen when the vessels are constricted and the blood flow is normal or rapid and the *leaden ashen cyanosis* is observed wl en there is a slow cutaneous blood flow with constriction of the superficial vessels

SKIN TEMPERATURE—Skin temperature depends mostly upon the volume of blood flow since the radiation of body heat is carried out principally through the medium of the cutaneous vessels The warmer blood of the deeper body areas is diverted through cutaneous channels where it becomes cooled in its passage

type of galvanometer is portable and considerably less expensive than the string model

THE ELECTROCARDIOGRAM

The electrocardiogram is a record of the currents generated by the cardiac contractions as recorded over standard leads

The Standard Leads—Clinical electrocardiography is accomplished by recording currents flowing through electrodes applied to arms left leg and precordium

In *Lead 1* the right and left arms are used for *Lead 2* the right arm and left leg are connected for *Lead 3* the left arm and leg are employed For the precordial leads the right arm electrode is placed on the left leg and the left leg electrode is put over various positions of the precordium

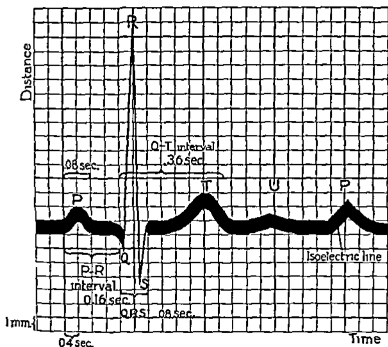


Fig 132 —Diagram of normal electrocardiogram

in the fifth intercostal space For *CF 2* the precordial electrode is placed at the left parasternal line for *CF 4* the electrode is placed in the mid clavicular line and for *CF 5* in the anterior axillary line

Before application of the electrodes the resistance of the skin is diminished by vigorous inunction with a jelly impregnated with salt

The Record—The paper on which the deflections are reproduced is a graph divided into millimeter squares by vertical and horizontal rulings The *horizontal* lines are time markers in units of 0 04 second Every fifth line is heavier and represents 0 20 second The *vertical* rulings indicate voltage The smallest divisions are 1 mm and the heavier lines 5 mm With the machine properly standardized 1 millivolt of current should deflect the string a distance of 10 mm

In malignancy however the lymphatics assist in the dissemination of the neoplastic cell (p 572)

The lymphatic apparatus is distributed very widely in subcutaneous tissues skin, subserosa and submucosa of the alimentary canal and the genito-urinary tract, capsule of liver and its septa and probably in muscle tissue There are no lymphatics in the central nervous system Scattered along the lymphatic vessels at various points are the *lymph nodes* some of these are deep but others are superficial and accessible to the palpating hand

See *Lymphadenopathy* (p 1136)

The Thoracic Duct—The lymphatics of the intestinal villi (the lacteals) have a specialized function for the absorption of digested fats their contents are collected in the *thoracic duct* which passes through the thorax to empty into the left subclavian vein

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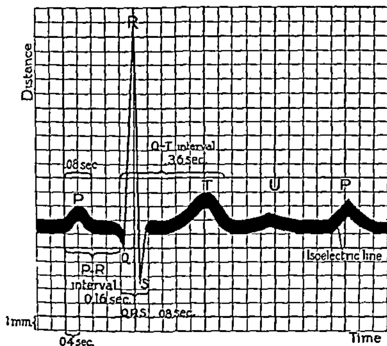


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3 0 3 cc (5 minims) of ether C P is mixed with 0 6 cc (10 minims) of sterile physiological saline solution
4 With a stopwatch kept directly in the line of vision the operator injects the ether rapidly into an antecubital vessel
5 The patient is directed to report the instant the odor of ether is detected this observation is checked by the operator who smells the breath

Normal and its Variations—The normal ether circulation time varies between 3 5 and 9 seconds When it is *prolonged* beyond this it may be assumed that there is right heart failure or decreased pulmonary aeration causing a retardation in the rate of diffusion of ether from the lungs

Untoward Reactions—Ether injections may cause local venous reactions particularly if they are given into a vein which has previously been used for saccharin or decholin In patients who suffer from the tetralogy of Fallot peripheral paresthesias may be felt

Taste Time—The taste time is most conveniently performed with a solution of saccharin made by dissolving 2 5 gm of soluble saccharin in 2 5 cc of sterile distilled water The mixture is heated but not boiled and then is cooled to room temperature before injection

Technic—

1 The saccharin solution is taken up into a syringe attached to an 18 gauge needle the blood pressure cuff is inflated to a reading of 40 mm of mercury
2 The needle is inserted into an antecubital vein the cuff is deflated and a period of half minute is allowed to elapse
3 The saccharin solution is injected rapidly into the blood stream
4 The patient reports immediately when the sweet taste of the test substance is noted
5 The normal saccharin time varies between 9 and 16 seconds
6 The saccharin time minus the ether time gives the circulation time for the left circuit

Interpretation—A prolongation of the saccharin time suggests left heart failure particularly if the ether time is normal A rapid circulation time is seen in hyperthyroidism and arterio venous shunts

DETERMINATION OF VENOUS PRESSURE

Inspection of the veins on the back of the hand as the outstretched arm is raised above the level of the heart is the simplest method of estimating venous pressure Under normal circumstances the veins collapse at the cardiac level If venous pressure is unduly elevated the level at which the veins collapse parallels the height of the pressure

Technic—Venous pressure may be measured directly with an 18 gauge needle a special adapter and two way stopcock a 20 cc syringe and an upright manometer tube with a 4 mm bore graduated in centimeters

1 The patient rests in recumbency for 15 minutes
2 The arm is supported on a pillow so that it is 5 cm below the level of the anterior chest wall

card or repeat the tracing in which 1 millivolt does not deflect 10 mm

3 Determine the *heart rate* and the relationship between the auricular and ventricular components Calculate by counting vertical lines each equaling 0 04 second Thus if R R measures 25 lines the time interval is 25 x 0 04 = 1 second and so the minute rate is 60 if 50 lines the interval is 50 x 0 04 = 2 seconds and the rate is 30 if 12 lines the interval is 12 x 0 04 or 0 48 and the rate approximates 120

4 Examine the *P waves* and measure the *P R interval*

5 Examine the *QRS complexes* with respect to duration shape amplitude and electrical axis

6 Examine the *T wave*

7 Measure the *S T segment*

8 State the *rate* and *rhythm* and describe any abnormalities that are present

Interpretation—The interpretation of the electrocardiogram is of great value in diagnosis prognosis and the establishment of indications for therapy As in the instance of all other laboratory information the electrocardiogram cannot be evaluated with accuracy until the record is regarded as a single item in the consideration of the problem as a whole Each electrocardiographic record is as unique for the particular individual as his fingerprints and there are no two records that are absolutely identical The practitioner who has the opportunity of living his life with his patients can often serve his medical charge in no better stead than by insistence upon the annual recording of an electrocardiogram after the age of 35 By this step an individual standard is established and deviations from the norm are the more easily appreciated

Normal Abnormalities—The recording of routine electrocardiograms illustrates to the practitioner a number of normal abnormalities Differences may be noted in cardiac rate and rhythm deviations may be observed in the P QRS and T complexes in the absence of any history or clinical evidences of circulatory difficulty The normality of these abnormalities is easily demonstrable through the fact that they do not change from week to week from month to month or year to year The enthusiasts for electrocardiography seeing these aberrations for the first time often tend to overinterpret them as evidences of coronary or myocardial damage such rashness results in irreparable damage through a gloomy diagnostic estimate and a resultant cardiophobia Typical tracings of normal abnormalities appear in the Atlas on page 811 For convenience they are listed below

Normal left axis deviation small Q_1 and Q_4 R T_4 elevated U wave present in third and fourth beats of Lead 4 See ECG 1 p 811

Deep Q_3 with deep inversion of T_3 See ECG 2 p 812

Normal axis deviation P_3 and T_3 deeply inverted R-T slightly elevated. See ECG 3 p 812

Normal left axis deviation R T_1 slightly depressed and R T_3 slightly elevated P_3 and T_3 inverted T_4 bifid See ECG 4 p 813

Sinus tachycardia of 130 tendency to right axis deviation R-T and R-T_3 moderately depressed T_3 inverted See ECG 5 p 813

TABLE 52—NUMBER OF TRIPS TO BE PERFORMED IN THE "TWO-STEP TEST" ARRANGED ACCORDING TO SEX, AGE AND WEIGHT

Weight (lbs)	Age (yrs)												
	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69
						Males							
40- 49	35	36											
50- 59	33	35	32										
60- 69	31	33	31										
70- 79	28	32	30										
80- 89	26	30	29	29	29	28	27	27	26	25	25	24	23
90- 99	24	29	28	28	28	27	27	26	25	25	24	23	22
100-109	22	27	27	28	28	27	26	25	25	24	23	22	22
110-119	20	26	26	27	27	26	25	25	24	23	23	22	21
120-129	18	24	25	26	27	26	25	24	23	23	22	21	20
130-139	16	23	24	25	26	25	24	23	23	22	21	20	20
140-149		21	23	24	25	24	24	23	22	21	20	20	19
150-159		20	22	24	25	24	23	22	21	20	20	19	18
160-169		18	21	23	24	23	22	22	21	20	19	18	18
170-179			20	22	23	23	22	21	20	19	18	18	17
180-189			19	21	23	22	21	20	19	19	18	17	16
190-199			18	20	22	21	21	20	19	18	17	16	15
200-209				19	21	21	20	19	18	17	16	16	15
210-219				18	21	20	19	18	17	17	16	15	14
220-229				17	20	20	19	18	17	16	15	14	13
						Females							
40- 49	35	35	33										
50- 59	33	33	32										
60- 69	31	32	30										
70- 79	28	30	29										
80- 89	26	28	28	28	28	27	26	24	23	22	21	21	20
90- 99	24	27	26	27	26	25	24	23	22	22	21	20	19
100-109	22	25	25	26	26	25	24	23	22	21	20	19	18
110-119	20	23	23	25	25	24	23	22	21	20	19	18	18
120-129	18	22	22	24	24	23	22	21	20	19	19	18	17
130-139	16	20	20	23	23	22	21	20	19	19	18	17	16
140-149		18	19	22	22	21	20	19	19	18	17	16	16
150-159		17	17	21	20	20	19	19	18	17	16	16	15
160-169		15	16	20	19	19	18	18	17	16	16	15	14
170-179		13	14	19	18	18	17	17	16	16	15	14	13
180-189			13	18	17	17	17	16	16	15	14	14	13
190-199			12	17	16	16	16	15	15	14	13	13	12
200-209				16	15	15	15	14	14	13	13	12	11
210-219				15	14	14	14	13	13	13	12	11	11
220-229				14	13	13	13	13	12	12	11	11	10

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TABLE 53—THE ANALYSIS OF NORMAL AND ABNORMAL ELECTROCARDIOGRAMS (*Cont d*)

Wave or Interval	Normal	Abnormalities (Numbers in parentheses refer to electrocardiograms in Atlas p 811–850)
T wave	Termination of ventricular systole *Usual height 1 mm*	Isolated T wave changes of inversion prominence flattening and deformity not diagnostic *Inversion in transverse position of heart* (2 3 49) Flattening or inversion by digitalis (61 69 70 71 73 74) Inversion in extracardiac conditions such as pneumonia, uremia, typhoid fever acidosis alkalosis (48) acute glomerulonephritis (31 43) status asthmaticus (24) and Addison s disease Inversion in left axis deviation (4 20 21) and right axis deviation (26) Inversion in coronary insufficiency (11 12) pulmonary embolization (15) and pericardial effusion (16 17 46) Inversion in coronary occlusion and myocardial disease (6 7 8 9 10 41 42) with anterior and posterior wall infarctions and right and left bundle branch blocks Inversion in myocarditis from rheumatic fever (45) and trichinosis (47)
RS-T interval	Iso-electric period in ventricular systole	May be slightly elevated or depressed in normals (3 4) May be depressed by digitalis (61 69 70 71) May be elevated in pericardial effusion (*16*) May be altered in pulmonary embolization (15) May be altered in left axis deviation (19 20) Chronic changes indicate myocardial damage (20 67) Acute changes combined with T abnormalities in coronary insufficiency (11 12 13 14 64 66) *and coronary occlusion* (6 7 8 9)
QT	Total ventricular systole Duration 0.36 seconds	See Q R S QRS and T Prolongation in chronic glomerulonephritis and from quinidine (75)
RR	Duration of single heart beat if of 1 second duration rate is 60	See Bradycardia, Tachycardia and Cardiac Arrhythmias (p 8 3)

Normal left axis deviation See **ECG 18** p 820
Slurring of QRS_1 and QRS but insufficient for diagnosis of myocardial damage See **ECG 33** p 8 7
Inversion of T and T_3 See **ECG 49** p 835

Extracardiac Changes—Alterations may be produced in the electrocardiogram by conditions that have little or nothing to do with the circulatory apparatus Profound changes are produced by acidosis alkalosis and *shifting* of the cardiac axis through ascites dilatation of the stomach changes in position a pleural effusion or a pulmonary atelectasis Digitalization is capable of the production of significant and widespread aberrations in the trace and quinidine may produce other abnormalities

whiskey A rough estimate of the effect can be obtained by the use of the oscillometer or the determination of claudication time if facilities for determining skin temperature are not available The *claudication time* is the duration or distance that the patient can walk before cramps in the leg supervene In vasospastic disorders claudication should occur more slowly after alcohol

DIAGNOSTIC ROENTGENOLOGY

Fluoroscopy *The Cardiac Contour*—The practitioner who possesses a fluoroscope is in a position to obtain invaluable information relative to the size and shape of the heart and great vessels Observations in postero anterior and left and right anterior oblique positions may be used to



Fig 119—Cardiac silhouette of normal male 44 years of age Postero anterior view

delineate the chambers of the heart and the contours of the aorta and pulmonary arteries (Figs 119 to 127 inclusive)

POSTERO ANTERIOR VIEW—In the postero anterior position the *right side* of the cardiovascular shadow comprises two curves convex to the right and composed of the right auricle below and the ascending aorta above

On the *left side* the uppermost shadow is the projecting convex knob of the aorta and the pulmonary artery while the lower three fifths or more of the left border is contributed by the *left ventricle* which slants to the left and down Systolic (inward) pulsations of the left ventricle are opposite in direction to synchronous pulsations of the pulmonary artery The boundary between these structures is indicated by the point of opposite pulsations

Partial heart block and occasional ventricular premature beats from ill advised prophylactic *digitalization* in a patient suffering a fracture of the femur See ECG 72 p 847
Partial heart block due to suicidal attempt taking 1 0 grams of *digitalis* See ECG 73 p 847
Ventricular tachycardia with multifocal ventricular pacemaking due to *digitalis* intoxication See ECG 74 p 848
Prolongation of Q T interval from doses of 0 4 gm of *quinidine sulfate* taken every 3 hours See ECG 75 p 848
Widening of QRS complexes due to toxic effects of *quinidine* on the interventricular conduction system See ECG 76 p 849
Effects of tobacco (p 3880)

The Diagnostic Electrocardiogram in Circulatory Disturbances—Certain electrocardiographic patterns are almost pathognomonic of many of the most profound circulatory disturbances The more important are listed below The numerals refer to tracings in the electrocardiographic Atlas which follows

Transverse Position of Heart (1 2)
Left axis deviat on with inverted P and T waves in Lead 3

Vertical Position of the Heart
Small R_1 w th h gh R and R_3 moderate right ax s de ation (5 44)

Dextrocardia
Mirror image

Inc eased Left Ventricular Work (1 2 3 4 18 19 20)
Increase of left a is dev at on increase of voltage of QRS beyond 17–20 mm R T_1 depressed R T_3 elevated T_1 inverted QRS widened up to 0 12 second

Increased Right Ventricular Work (5 21 22 23 24 25 26 27 70 77)
Increase of right axis dev ation dep ession of R T_2 and R T_3 nve s ons of T and T_3

Mitral Disease (25 26 29)
P waves widened notched and of incr ased voltage

Acute Rheumatic Carditis (45)
Prolongation of P R interval

Acute Coronary Insuff c ency (11 12 13 14 64 82)
R-T *segment d pressions in on or several leads T wa in ers ns changes transitory* and revers ble

Anter or Wall Infarct on (6 7 10)
Q_1 and Q_4 present *ele at o s of R T_1 and R T_4 compensatory d press on of R T_3* inversion of T_1 and T_4 w dening of QRS

Posterior Wall Infarction (8 9 10)
Q_2 and Q_3 present elevations of R T_2 and R T_3 compensatory depressions of R-T_1 and R-T_4 T_2 and T_3 may become inverted arrhythmias frequent

Left Bundle Branch Block (36 72)
Left axis deviation QRS notched and wid ned beyond 0 12 second R T_1 depressed R T_3 elevated T_1 inverted



Fig 121 —Cardiac silhouette of normal male 44 years of age Left anterior oblique view



Fig 122 —Cardiac silhouette Postero-anterior view showing prominence of middle segment of left cardiac border This is due to elevation of main pulmonary artery resulting from right ventricular enlargement. Elderly patient with emphysema, pulmonary fibrosis and bronchial asthma.

Auricular Fibrillation (23 51 64 65 70 71)

Irregular deflections represent the auricular activity which is usually at a rate of 400 to 500 to the minute unless there is complete auricular ventricular dissociation the ventricular rate is completely irregular

Ventricular Tachycardia (66 74)

The ventricular rate is below 200 and the QRS complexes appear as rapid succession of premature ventricular beats spaced slightly irregularly

Ventricular Fibrillation (68)

Since this irregularity is almost invariably terminal observations are rare they consist of irregular oscillations of the beam of the galvanometer

Auricular Ventricular Conduction Defects (62 70 72 73 77 78 79 80)

First degree heart block consists of prolongation of P R second degree heart block is present if every auricular contraction does not have a ventricular response the block may be 2-1 3-1 4-1 5-1 etc second degree block is usually an expression of myocardial disease coronary artery disease or rheumatic carditis the Wenckebach s period is present if the P R intervals become progressively longer preceding each dropped beat complete auricular ventricular dissociation is present if there is complete independence of auricular and ventricular mechanisms under these circumstances the QRS complexes may be normal or they may have the bundle branch block patterns

ATLAS OF ELECTROCARDIOGRAPHY

An Atlas of electrocardiography consisting of 80 tracings has been compiled As an exercise in the interpretation of this collection it is suggested that the practitioner familiarize himself with the preceding text and then proceed to analyze each electrocardiogram before reading the accompanying legends



ECG I —Male age 50 Regular sinus rhythm rate 64 P waves normal P R interval within normal limits left axis deviation of normal degree small Q_1 and Q_4 present U waves best seen in Lead 4

scopically, this is first evidenced by increased rounding of the left ventricle as seen in the *postero anterior view* and a downward elongation of the ventricle below the contour of the diaphragm Enlargement of the inflow tract (mitral valve to apex) follows that of the outflow tract and shows up best in the left anterior oblique position The posterior border becomes longer and bulges backward often crossing the spine and the interventricular notch is displaced forward Eventually, in the *postero-anterior position* the left contour of the heart appears to reach the chest wall

Aneurysm of the left ventricle resulting from myocardial infarction occurs most commonly in the region of the apex where it is best visualized with the chest in the position of maximal inspiration Aneurysms also

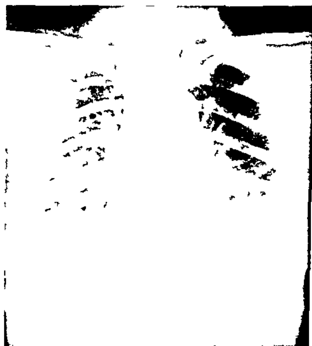
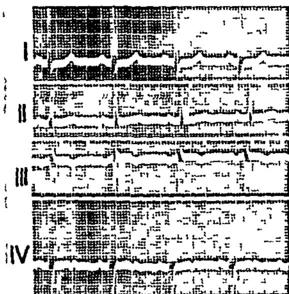


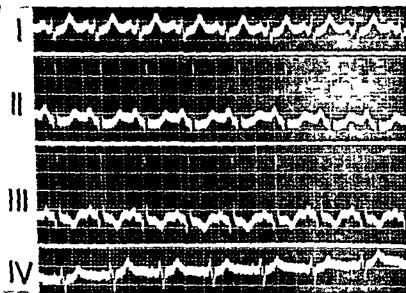
Fig 124—Cardiac silhouette antero-posterior view Woman of 39 with marked hypertension following toxemia of pregnancy at age 29 After 3 years of backward failure, heart shows considerable enlargement to left, prominence of branches of the pulmonary arteries and congestion of both lower lung fields

occur on the upper lateral and posterior walls of the left ventricle less commonly in the right ventricle Aneurysmal bulges are noted only if the patient is properly rotated and examined with the screen diaphragm closed so that only a small light field remains Except in the most obvious cases the aneurysm will not show as an outpocketing of the ventricular walls but rather will appear as a localized area in which the pulsation of the ventricular wall is opposite to that of the rest of the ventricle Thus when the main body of the ventricle moves inward in systole the location of an aneurysm will be marked by an outward localized pulsation This is commonly designated as reversal of pulsation

LEFT AURICLE—The left auricle lies chiefly on the posterior aspect



ECG 4.—Female age 60 blood pressure 180/100 moderately obese Regular sinus rhythm left axis deviation R T_1 very slightly depressed R T_3 very slightly elevated P_3 and T_3 inverted T_4 bifid This electrocardiogram has no positive diagnostic value The left axis deviation is insufficient evidence to assume increased left ventricular work and may be due to a transverse position of the heart



ECG 5.—Female age 21 neurocirculatory asthenia (autonomic imbalance) Sinus tachycardia of 130 tendency to right axis deviation R T and R T_2 are moderately depressed T_3 is inverted The changes due to the vertical position of the heart may be confused evidences of beginning increased right ventricular work

THE AORTA —Dilatation and elongation of the aorta are best observed in the *left oblique* view The descending limb is pushed from its usual place in front of the vertebral column to the left paravertebral space The

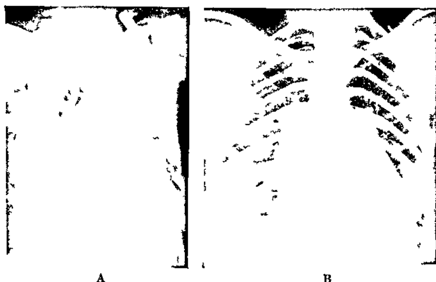


Fig 126—Cardiac silhouette *A* Right anterior oblique view Barium fills esophagus which is displaced posteriorly by the enlarged left auricle The left bronchus is elevated and narrowed The pulmonary artery segment is prominent due to elevation and anterior displacement by the left auricle *B* Postero anterior view Note enlargement of heart to left and right with special prominence of middle segment of left border

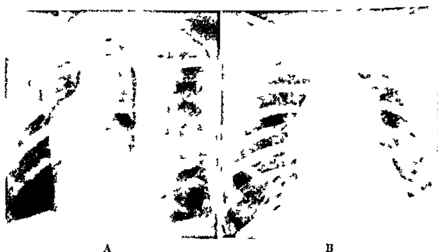
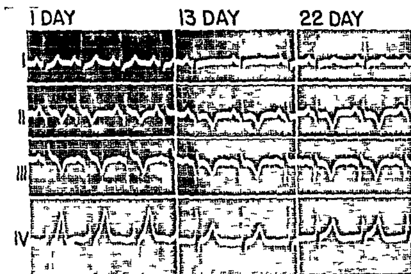


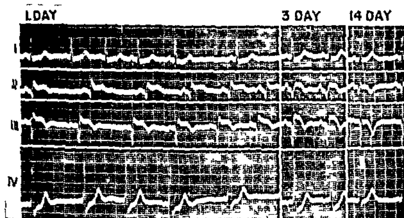
Fig 127—Aneurysm of ascending aorta in a male aged 50 *A* In this left anterior oblique view the sac can be seen more clearly *B* Postero-anterior view Note bulge to right of ascending aorta

esophagus is pulled backward and to the left by its attachment to the aorta The descending aorta best visualized in the *right anterior* oblique position may cause a curve convex to the left beneath the aortic knob Calcification is most prominent in the descending portion



ECG 8 —Male age 62 Symptoms of myocardial infarction 48 hour prior to admission

1st day Regular sinus rhythm auricular premature contraction in second beat lead 2 deep Q_2 and Q_3 R T and R T_3 elevated R T and R T_4 depressed T_2 and T_3 inverted changes characteristic of acute posterior wall infarction due to coronary artery occlusion *13th to 22nd day* Gradual disappearance of R T segment deviations progressive T wave inversions the transient lowering of T_1 has no significance



ECG 9 —Male age 60 Brief periods of moderate precordial pain 2 hours before first electrocardiogram

1st day Marked sinus arrhythmia deep Q and Q_3 present R T_2 and R T_3 elevated R T_1 and R T_4 depressed T_3 semi inverted change characteristic of acute posterior wall infarction due to coronary artery occlusion alterations of the regular sinus mechanism are most fre

Dilatation of the superior vena cava appears as a beltlike shadow to the right of the sternum lying parallel to or above the ascending aorta in the postero anterior views

If the exact nature of a mediastinal mass cannot be determined by the usual roentgenologic method the intravenous injection of diodrast a radiopaque substance may reveal whether the lesion is extravascular or continuous with the vascular tree This method is not suitable for the practitioner since it requires special x ray equipment

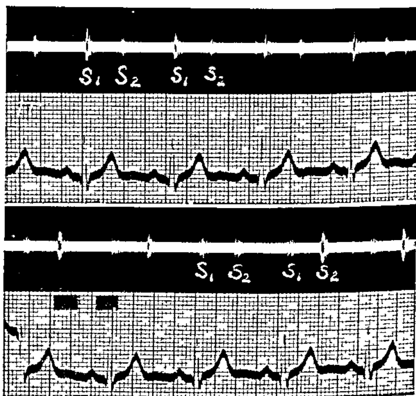
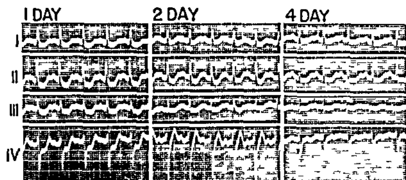


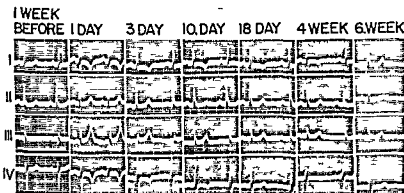
Fig 129—Normal heart sounds Simultaneous phonocardiograms and electrocardiograms of a normal male 29 years of age The upper sound curves were taken from the apex and the lower from the pulmonary area Note that the first sound (S_1) is louder at the apex and fainter at the base than the second sound (S_2) The relative intensity of the two sounds varies both in normal and abnormal hearts *

Orthodiagraphy—Orthodiagraphy is carried out by tracing the outline of the heart and great vessels on the fluoroscopic screen with the aid of a movable x ray tube This allows various parts of the heart to be exposed to the central rays thereby eliminating distortion The method has the advantage of giving a cheap permanent record of the heart size It requires considerable training however and is not entirely objective even in experienced hands Where expense is an important factor orthodiagraphy may be used in preference to *teleoroentgenography* but by and large the latter method is the more satisfactory

* Levine, Clinical Heart Disease.



ECG 11 —Male age 54 Acute gastro intestinal hemorrhage due to a duodenal ulcer onset of severe precordial pain and shock
1st day Sinus tachycardia of 135 R T segments markedly depressed *in all leads* T_1 *and* T_3 *diphasic changes indicate acute coronary insufficiency* *2nd day* Condition worse development of backward failure R T segments less depressed *4th day* Day of death digitalis had been given after the second record still more regression of R T segment depressions
Comment Classical example of acute coronary insufficiency



ECG 12 —Female age 53 Essential hypertension for 3 years angina pectoris *for 1 year uterine bleeding for 3 months* While under observation patient developed a profuse uterine bleeding with severe precordial pain No subsequent drop of blood pressure elevation of temperature to 100 8° F
1 week before Essentially normal electrocardiogram *1st day* R T_1 and R T_4 slightly depressed T_1 and T_4 deeply inverted changes indicate acute coronary insufficiency *3rd day to 4th week* Gradual regression of R T and T changes *6th week* Normal electrocardiogram
Comment In contrast to *ECG 11* T wave changes more pronounced than R T segment deviations

chines are designed so that the practitioner may record simultaneously the electrocardiogram and the phonocardiogram or stethogram

The Normal Stethogram —Examination of the normal stethogram (Fig 129) reveals that the *first heart sound* occurs simultaneously with the R wave the *second sound* corresponds with the end of the T wave the *third sound* if present is 0 011 to 0 014 seconds after the beginning of the second sound, the *auricular sound* is placed between the P and Q waves of the cardiogram Between the first and second sounds there is a smooth base line which represents systole following the second sound a similar appearance represents diastole

Abnormalities —The recording of *cardiac murmurs* is rarely of great clinical significance The important abnormalities in sound are audible to the normal ear while those which cannot be heard by ordinary methods are probably of little or no clinical significance The classical murmurs of *mitral stenosis* and *aortic insufficiency* are depicted in the accompanying illustrations (Figs 130 and 131) Other than for record purposes and clinical teaching these tracings have little importance for the practitioner

ELECTROCARDIOGRAPHY

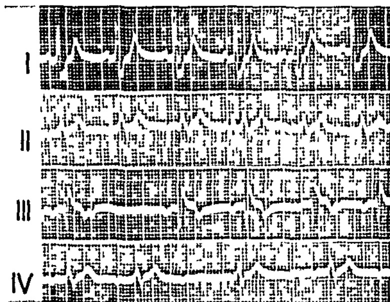
Electrocardiography is an indispensable portion of the modern cardiac examination The instrument records the action current which spreads through the heart with each contraction The practitioner may record th electrocardiogram by the use of the string or oscillograph galvanometer

The string galvanometer is an electromagnet whose north and south poles enclose a concentrated magnetic field A fine quartz string (0 004 mm in width) covered with silver or platinum is suspended between the two poles As an electric current is passed through this string (a conductor) it moves perpendicularly to the lines of force of the magnetic field It will move in one direction or the other depending on whether the current passes up or down the conductor The amplitude of the movement depends on (1) the strength of the magnetic field (2) the strength of the current and (3) the tension of the string

An electric light and a condenser illuminate the movements of the string which are magnified about 500 times by a microscope At fixed intervals the light is interrupted by a timing device which permits the accurate measurement of time relationships The shadow of the illuminated string is recorded by a camera containing a roll of film or bromide paper which is unrolled by a small motor and which passes before an aperture opened and closed by a simple shutter There is also a device for varying the tension on the galvanometer string so that when 1 millivolt of current is passed through it the shadow will deflect 1 cm This is known as the *standardization of the tracing*

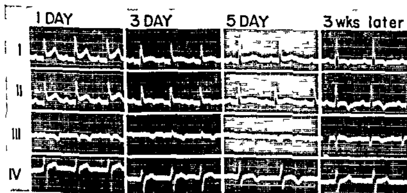
The oscillograph type of galvanometer is as sensitive as the string variety It depends on vacuum tube amplification and consists of a small mirror attached to a coil suspended in a magnetic field with a three stage amplifier in the input circuit A beam of light reflects from the mirror to a moving photographic surface Calibration is produced by adjustment of the sensitivity of the amplifier so that the introduction of one millivolt in the input circuit deflects the light spot 1 centimeter The oscillograph

Before exercise No abnormality *1 minute after exercise* R T₂ and R T_3 markedly depressed *2 minutes after exercise* R T_2 less depressed Changes indicate exertional coronary insufficiency due to coronary artery disease



ECG 15—Male age 48 Collapse 10 days postoperatively with cyanosis and development of right heart failure

Regular sinus rhythm with occasional Wenckebach periods and blocked auricular premature beats (L III) QRS widened to 0 11–0 12 sec deep S_1 and Q_3 present R T_1 slightly depressed R T_3 elevated T_3 inverted Changes suggest pulmonary embolism confirmed by postmortem examination



ECG 16—Male age 20 Recurrent rheumatic carditis with predominant pericarditis *1st day* Elevations of R T_1 R T_2 and R T_4 *3rd to 5th day* Regression of R T segment elevations lowering of T waves *3rd week* R T segments iso electric T waves inverted in the standard leads Classical changes of acute pericarditis

The Normal Waves—The normal electrocardiogram consists of a series of five waves designated arbitrarily by the letters P Q R S and T Each wave is an upward (*electropositive*) or downward (*electronegative*) deflection from the isoelectric base line In the various leads the waves differ in form but the same general configuration and sequence is recognizable throughout

The P R and T waves are normally electropositive and upright (above the isoelectric line) in all leads The T wave in Lead III is frequently inverted (electronegative) and below the isoelectric line The Q and S waves are usually small negative deflections

The P R and T waves are the more constant deflections and are greatest in Lead II which is the sum of the heights of the waves in Leads I and III In normal persons the complexes vary considerably from individual to individual and considerable experience is required before slight deviations can be critically analyzed It is important to recognize that electrocardiographic contours vary with age of the patient the position of the body the phases of respiration and the physical habitus of the individual

The P Wave—The P wave represents the electrical changes occurring in auricles It is usually 0 08 second in duration and less than 2 mm in height Its shape tends to be blunt and round but may be pointed

The QRS Complex and T Wave—The Q R S and T waves are due to ventricular action currents and are divided into the initial deflections (QRS) and the terminal deflection (T)

The *QRS complex* consists of a short downward (negative) deflection (*Q*) a sharp upward deflection (*R*) and a second short downward deflection (*S*) The amplitude of the R wave is from 7 to 15 mm and the duration of the complex is 0 08 second The QRS complex measures the spread of the electrical impulse through the ventricles via the bundle of His the subendocardial Purkinje fibers and the thickness of the heart muscle

The *T wave* is a smooth rounded curve measuring 1 to 5 mm in height The T wave represents the retreat of the electric impulse with relaxation of the muscle

In addition to the five large waves a sixth or U wave may be seen between T and P It has no clinical significance

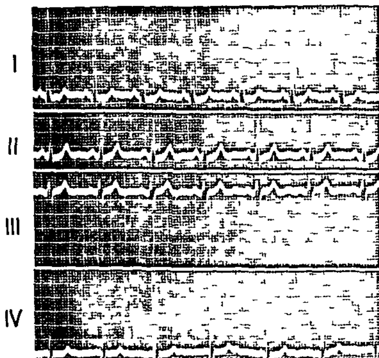
The Time Intervals—The time interval from the beginning of the P wave to the beginning of the R wave (*P R interval*) is a measure of the auriculo ventricular conduction time and normally is 0 16 second

The segment between the end of the QRS and the T wave (R T S T) is normally *isoelectric* or 0 05 mm above or below the isoelectric line The duration of the *Q T interval* is an accurate measurement of the length of electrical systole (0 36 second)

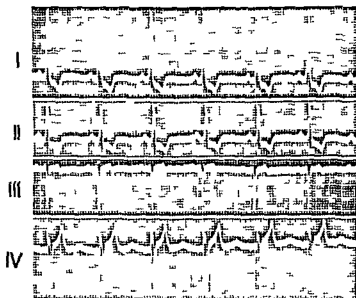
Routine of Electrocardiographic Interpretation

A routine procedure should be followed during the inspection of an electrocardiogram The following sequence will prove helpful

1 *Enumerate the leads* and check their labeling
2 Note any *artefacts* Observe the *standardization of the string* Dis



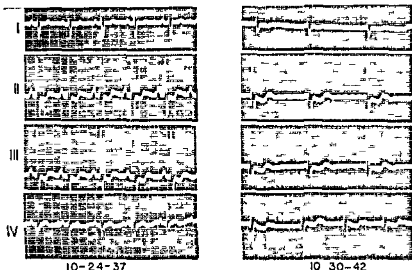
ECG 19 —Male age 51 essential hypertension Marked left axis deviation QRS of very high voltage R T_1 slightly depressed Changes indicate increased left ventricular work



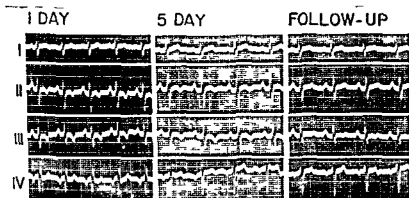
ECG 20 —Male age 33 malignant hypertension Marked left axis deviation QRS of high voltage R T_1 and R T_2 depressed T_1 and T inverted Changes indicate left ventricular enlargement with myocardial damage

Table 53—The Analysis of Normal and Abnormal Electrocardiograms

Wave or Interval	Normal	Abnormalities (Numbers in parentheses refer to electrocardiograms in Atlas p. 811 ff.)
P wave	Produced by auricular systole Duration of 0.08 seconds Height of 2 mm	Isolated P wave abnormalities have little diagnostic significance P_3 may be inverted in transverse position of heart (3) P may be widened, notched and of increased voltage in mitral disease (25, 26, 29) P may be high and peaked but not notched in pulmonary afflictions (22, 27) P may be prominent in right axis deviation with congenital cardiac disease (23) P may be prominent in coronary occlusion P may be prominent in a variety of extracardiac conditions such as pneumonia, hypertension and hyperthyroidism (28)
P-R interval	Represents auriculo-ventricular conduction time Iso-electric period of a duration of 0.16 seconds	Elevations and depressions of PR of no clinical significance Prolongation most often due to digitalis, acute rheumatic fever (15) or arteriosclerotic heart disease, less often to acute glomerulonephritis or typhoid fever or other acute infectious diseases
Q wave	Initial downward deflection of ventricular systole (See also QRS)	Small Q waves may be present in normals (1, 2) Appearance of Q_1 and Q_4 suggests anterior wall myocardial infarction (6, 7, 10) Appearance of Q and Q_3 suggests posterior wall myocardial infarction (8, 9)
R wave	Initial upward deflection of ventricular systole (See also QRS) Height varies from 7 to 20 mm	$R = R_1 + R_3$ R_1 of high voltage and in excess of R_2 suggests left axis deviation (1, 2, 3, 4, 18, 19, 20) R_1 of low voltage in right axis deviation (5, 21, 22, 23, 24, 25, 26, 27, 70, 77)
S wave	Second downward deflection of ventricular systole (See also QRS)	S_3 prominent in left axis deviation
QRS complex	Total ventricular systole except for T wave Duration 0.08-0.10 seconds	Changes most significant in QRS_1 and QRS. See Q, R and S May be slurred without evidences of heart disease (33, 34) Widening from quinidine (76) and large doses of digitalis Low voltage in myocardial damage due to coronary disease (35, 42), in hypothyroidism, Addison's disease and pericardial effusion (46) High voltage in hypertension with marked left axis deviation (19) Widening and notching in pulmonary embolization (13), left bundle branch block (36, 72), right bundle branch block (37, 77), myocardial damage from coronary artery disease (38, 39), heart block (77, 80) and rheumatic carditis (63) May be slightly deformed in extracardiac afflictions such as acute infections, scarlet fever and hepatitis (32)



ECG 23 —Female age 39 intra auricular septal defect with advanced congestive heart failure *First ECG* Regular sinus rhythm markedly prominent P waves marked right axis deviation with high voltage of QRS R T and R T_3 depressed T_2 and T_3 diphasic changes are indicative of increased right ventricular work high voltage of QRS frequently seen in RAD due to a congenital cardiac lesion *Second ECG* Auricular fibrillation now present with high degree of AV conduction defect Digitalis had been given



ECG 24 —Male age 39 status asthmaticus *1st day* Sinus tachycardia of 120 T and T_3 inverted deep S waves in standard leads changes suggest acute cor pulmonale *5th day and follow up record* Gradual disappearance of T wave abnormalities

Drug changes are often most confusing since therapy is often instituted before the electrocardiogram has been taken and it may then be impossible to differentiate the disturbances due to the drug from those that are the result of the fundamental circulatory lesion

Electrocardiographic Changes Due to Extracardiac Causation

Obesity with transverse position of heart produces *left* axis deviation and deep inversions of P_3 and T_3 with slight elevation of R-T See ECG 3 p 812

Neurocirculatory asthenia results in sinus tachycardia of 130 with tendency to right axis deviation moderate depression of R T inversion of T_3 See ECG 5 p 813

Duodenal ulcer with *acute hemorrhage* produces evidences of acute coronary insufficiency See **ECG 11** p 817

Uterine bleeding in a woman with essential hypertension produces evidences of acute coronary insufficiency See **ECG 12** p 817

Pulmonary embolism produces partial heart block, widening of QRS depression of R T_1 elevation of R T_2 and inversion of T_3 See **ECG 15** p 819

Prominent P waves and marked right axis deviation in chronic cor pulmonale due to *bronchiectasis* See **ECG 22** p 822

Sinus tachycardia, inversions of T_2 and T_3 with deepening of S waves in *status asthmaticus* See **ECG 24** p 823

P_2 and P_3 prominent in an attack of *bronchial asthma* See **ECG 27** p 825

Sinus tachycardia of 140 with prominence of P and P_3 in *hyperthyroidism* See **ECG 28** p 825

Prolongation of P R interval with T wave inversion in *acute glomerulonephritis* See **ECG 31** p 827

Notching of QRS, during an attack of *acute arsenical hepatitis* See **ECG 32** p 827

Deep inversion of T_1 and T_2 in *acute glomerulonephritis* See **ECG 43** p 832

Depression of R T_3 isoelectric T_1 diphasic T and T_3 and inversion of T_4 in *diabetic coma* See **ECG 44** p 833

Low voltage QRS and iso-electric T wave in *pericardial effusion* associated with *nephrosis* See **ECG 46** p 834

Depression of R T_2 and R T_3 with iso-electric T_1 in *alkalosis due to pyloric obstruction* See **ECG 48** p 835

Sinus bradycardia in vagotonic patients with *duodenal ulcer* See **ECG 51** p 836

Periods of sinus arrest in a patient with a *brain tumor* See **ECG 53** p 837

Supraventricular tachycardia occurring *following operation* See **ECG 59** p 840

Auricular fibrillation and evidences of coronary insufficiency *following mesenteric embolism* See **ECG 64** p 842

Electrocardiographic Changes Due to Drugs

Auricular ventricular conduction defect after *digitalization* in auricular fibrillation See **ECG 23** p 823

Therapeutic effect of *digitalis* in paroxysmal auricular flutter showing conversion to auricular fibrillation followed by restoration of regular sinus rhythm See **ECG 61** p 841

Control of auricular fibrillation by *slowing* of the ventricular rate due to *digitalis effect*. See **ECG 65** p 843

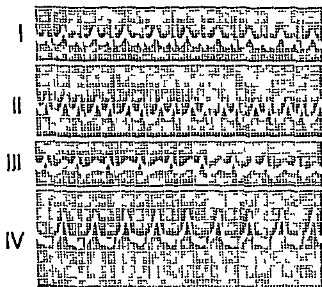
Depression of R T_2 and R T_3 and low voltage T waves probably due to prolonged administration of *digitalis* See **ECG 69** p 845

Auricular fibrillation high degree of A V dissociation and frequent ventricular premature beats with bigeminal rhythm and inversion of T_2 and T_3 while under the influence of *digitalis* after two weeks of abstinence from the drug only the slow auricular fibrillation persists See **ECG 70** p 845

Record A shows *digitalis* T wave record B after larger doses of the drug reveals marked depression of R-T_2 and R-T and a bizarre series of multifocal ventricular premature contractions See **ECG 71** p 846



ECG 27 —Male age 62 bronchial asthma *First ECG* Ectopic rhythm probably auricular tendency to right axis deviation *One week later* Sinus rhythm P waves now markedly prominent and peaked in Leads 2 and 3 Changes often seen in attacks of bronchial asthma



ECG 28 —*Female age 26 hyperthyroidism* Sinus tachycardia of 145 P_2 and P_3 *prominent Changes compatible with presence of hyper thyroidism*

Right Bundle Branch Block (37 77)

Right axis deviation QRS notched and widened R T_1 elevated R T_3 depressed or slurring and notching of S portion of QRS_1 Q_3 present (so-called Atypical Right Bundle Branch Block)

Coronary Artery Disease

See *Coronary Insufficiency Anterior and Posterior Wall Infarctions Right and Left Bundle Branch Block* also low voltage QRS (35) depression of R T and T wave changes (40)

Myocardial Damage

See *Anterior and Posterior Wall Infarctions Right and Left Bundle Branch Block, Rheumatic Fever*

Pericarditis (16 17, 46)

R T elevations in all leads T wave inversions appear later low QRS and T waves occasionally encountered often an associated auricular fibrillation or flutter

Pulmonary Embolism (15, 37)

As coronary insufficiency or sudden appearance of atypical pattern of Right Bundle Branch Block deep S_1 and Q_3 QRS notched and widened in S portion of Lead 1 R T_1 depressed R T_3 elevated T_3 inverted serial records show rapid disappearance of QRS widening and appearance of inversion of T_4

Sinus Tachycardia (5 21 24, 28 50)

P QRS and T complexes are complete and ventricular rate is above 100

Sinus Bradycardia (51)

P QRS and T complexes are complete and ventricular rate is below 60

Sinus Arrhythmia (52)

P QRS and T complexes are complete and ventricular rate is irregular

Sinus Arrest (53)

Failure of auricular beat

Auricular and Nodal Premature Beats (54 60 75)

The premature QRST complex usually simulates the normal QRS complex, it may be preceded by an upright or inverted P wave and the P R interval may be shortened or prolonged with nodal extrasystoles the P wave may not be recognized since it is included within the QRS complex in other instances there may be a negative P R interval in which the inverted P wave follows the QRS

Ventricular Premature Beats (72 71 70 67 55)

Ventricular extrasystoles usually have the pattern of a bundle branch block

Ectopic Rhythm (Wandering Pacemaker) (56 57)

An ectopic pacemaker in the sino auricular node is recognized by minor changes in the shape of the P wave if the pacemaker is in the region between the sino-auricular and the auricular ventricular node there are major alterations of P with inversion and the P R interval is shortened or negative

Ectopic Auricular Focus and Nodal Rhythm

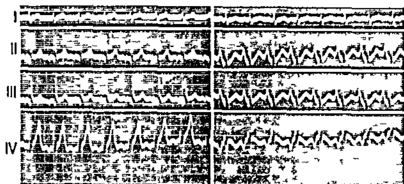
The P wave is inverted in Leads 1 and 2 or 2 and 3 P R is shortened or P may follow QRS the ventricular rate is usually below 60

Supraventricular and Nodal Tachycardia (59 60 67 76)

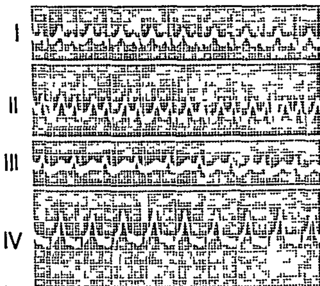
A rapid and regular succession of P waves are seen the QRS complex may be normal slightly or markedly aberrant

Auricular Flutter (61 62 63)

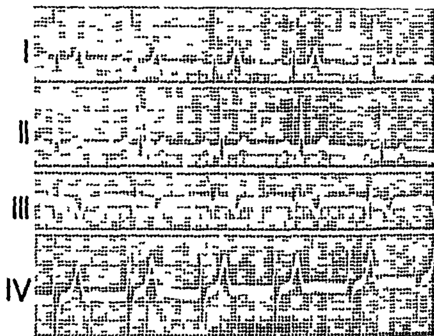
The flutter waves are regular serrated particularly in Leads 2 and 3 the ventricular response is usually 2 3 4 or 5-1 1-1 flutter may be followed by an aberrant QRS complex



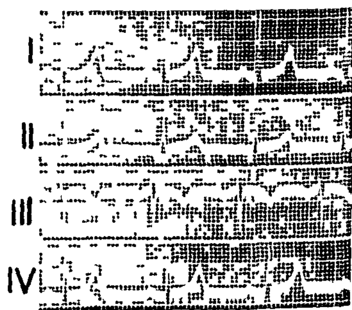
ECG 27 —Male age 62 bronchial asthma *First ECG* Ectopic rhythm probably auricular tendency to right axis deviation *One week later* Sinus rhythm P waves now markedly prominent and peaked in Leads 2 and 3 Changes often seen in attacks of bronchial asthma



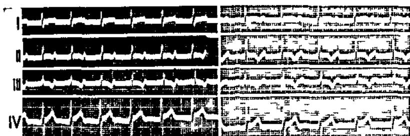
ECG 28 —Female age 26 hyperthyroidism Sinus tachycardia of 145 P and P_3 prominent Changes compatible with presence of hyper thyroidism



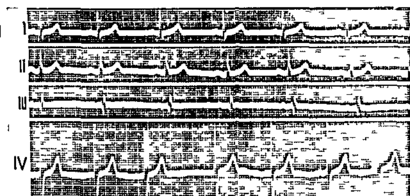
ECG 2—Female age 28 moderately obese Regular sinus rhythm deep Q_3 and inverted T_3 present should not be interpreted as revealing myocardial damage although the appearance is compatible with remnant of a previous posterior wall infarction



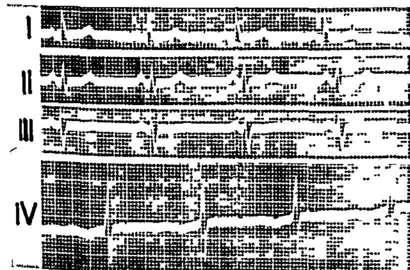
ECG 3—Female age 32 obese Regular sinus rhythm left axis deviation P_3 and T_3 are deeply inverted suggesting a transverse position of the heart



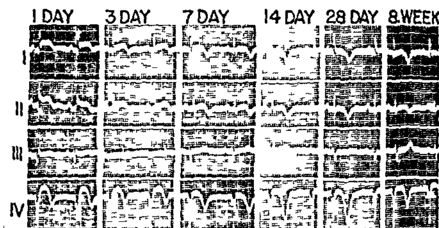
ECG 31 —Male age 28 acute glomerulonephritis P R interval prolonged to 0 38 sec in both records T wave inversions appear prolongation of P R interval infrequently seen in acute glomerulonephritis



ECG 32 —Male age 34 no heart disease Notching of the QRS after acute arsenic hepatitis

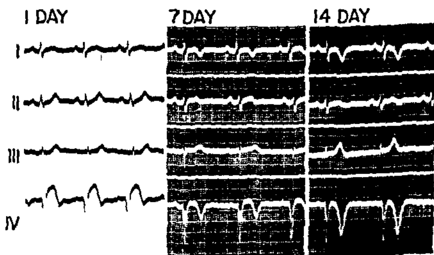


ECG 33 —Female age 50 no clinical evidence of heart disease QRS_1 and QRS slurred Findings insufficient for diagnosis of myocardial damage



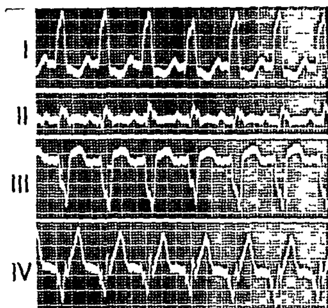
ECG 6 —Male age 49 Onset of symptoms 24 hours previously with crushing precordial pains

1st day regular sinus rhythm small Q_1 and deep Q_4 present R T_1 and R T_2 and R T_4 elevated T_1 and T_4 semi inverted changes characteristic of acute anterior wall infarction due to coronary artery occlusion *3rd day* decreasing elevations of R T_1 R T_2 and R T_4 increasing inversions of T_1 T_2 and T_4 *14th to 28th day* R T_1 R T_2 and R T_4 no longer elevated T_1 T_2 and T_4 deeply inverted and cove plane *8th week* T_1 T_2 and T_4 less inverted

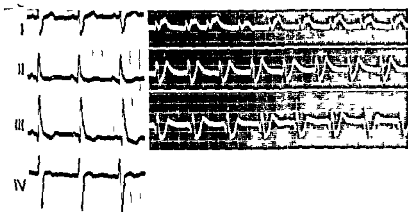


ECG 7 —Male age 39 Typical history of acute myocardial infarction 4 hours prior to first electrocardiogram

1st day Regular sinus rhythm deep Q_4 present R T_4 elevation T_4 semi inverted changes characteristic of acute anterior wall infarction due to coronary artery occlusion in spite of normal standard leads *7th to 14th day* Gradual disappearance of R T_4 elevation T_4 more deeply inverted and cove plane on the 14th day T_1 progressively inverted T_2 transiently semi inverted on the 7th day

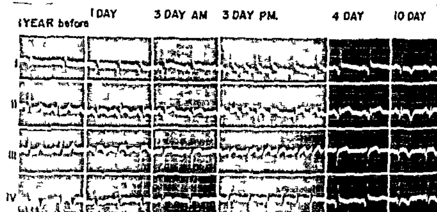


ECG 36—Male age 50 coronary artery disease Left axis deviation QRS high voltage slurred notched and measures 0 18 to 0 20 seconds QRS_4 polyphasic R T_1 depressed R T_3 elevated T_1 diphasic T_2 low T_3 semi inverted Changes indicate myocardial damage with left bundle branch block



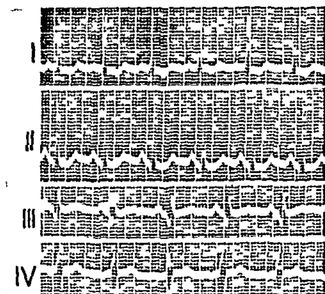
ECG 37—Female age 64 carcinoma of the breast *Preoperative record* Right axis deviation QRS slurred notched and widened to 0 14 to 0 16 second R T_3 slightly depressed T_2 low T_3 diphasic T_4 semi inverted Changes indicate myocardial damage with right bundle branch block *Second record* preterminally after huge pulmonary embolism Marked prolongation of the P R interval to 0 44 to 0 48 second occasional auricular premature contraction moderate degree of left axis deviation R T_2 and R T_3 markedly depressed Record of dying heart no diagnostic interpretation warranted

quently seen in posterior wall infarction *3rd day* Sinus arrhythmia no longer present, otherwise no significant change *14th day* R T and R T_3 only slightly elevated R T_1 no longer depressed, R T_4 much less depressed, T_2 semi inverted on the 3rd day now deeply inverted T_3 more deeply depressed

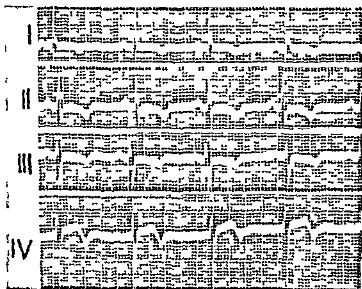


ECG 10 —Male age 45 Acute myocardial infarction two years ago recurrence of symptoms 24 hours prior to second electrocardiogram *1 year before* Regular sinus rhythm Q_1 present QRS_4 W shaped (equivalent to deep Q_4) T_1 diphasic T_4 deeply inverted changes indicate myocardial damage due to a previous anterior wall infarction caused by coronary artery occlusion *1st day* Sinus tachycardia of *120* Q_3 and Q_2 now present, T_2 and T_3 semi inverted T_4 diphasic changes indicate acute posterior wall infarction due to coronary artery occlusion *3rd day A.M* Patient has renewed severe episode of precordial pain and has gone into severe shock Q_1 now deeper R T_1 elevated R T_3 no longer elevated T_4 no longer inverted, changes indicate acute anterior wall infarction in addition to acute posterior wall infarction *3rd day P.M* Auricular fibrillation with rapid ventricular rate now present R T_1 and R T_2 more elevated Lead 4 now normal *4th day* Regular sinus rhythm again present (no digitalis had been given) R T_4 now elevated otherwise as on third day *10th day* All R T segment deviations disappearing T waves now inverted in all leads

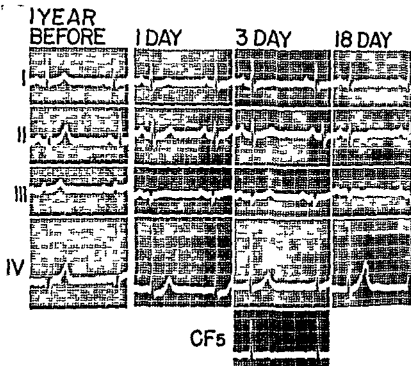
Comment Patient had an acute anterior wall infarction two years ago two acute infarctions occurred at this observation In spite of major damage to the myocardium patient made a rather satisfactory recovery



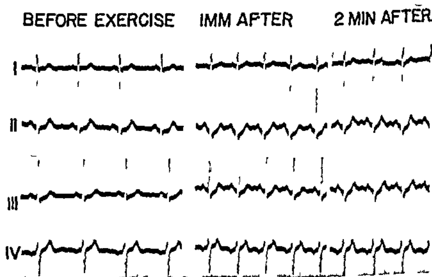
ECG 40 —Male age 63 coronary artery disease Regular sinus rhythm R T_1 and R T_2 depressed T_1 and T_2 diphasic T_3 low Changes indicate myocardial damage since no digitalis has been given



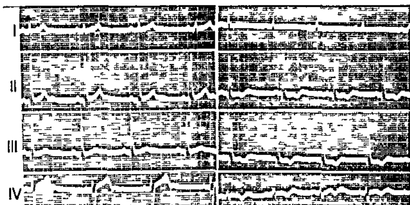
ECG 41 —Male age 58 coronary artery disease Regular sinus rhythm left axis deviation T waves inverted in all leads Changes indicate myocardial damage



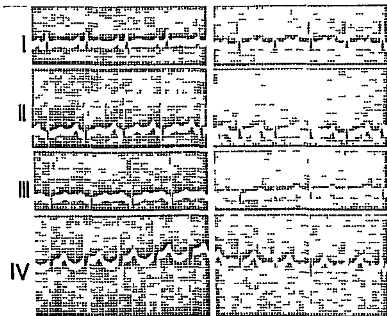
ECG 13 —Male age 38 Angina pectoris for 3 years severe attack lasting for about one hour 2 hours prior to second electrocardiogram *1 year before* Essentially normal electrocardiogram *1st day* R T_4 markedly depressed indicating acute coronary insufficiency *3rd to 18th day* Disappearance of R T_4 depression appearance of iso electric T_1 diphasic T_2 and semi inverted T in C F_5



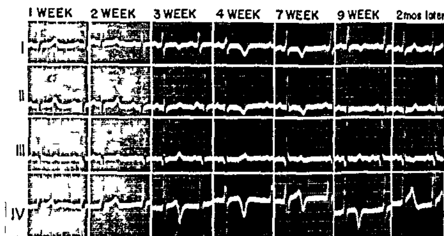
ECG 14 —Male age 42 Ill defined precordial distress for six months not related to effort occasionally after meals Patient quite nervous psychiatric consultant diagnosed conversion hysteria



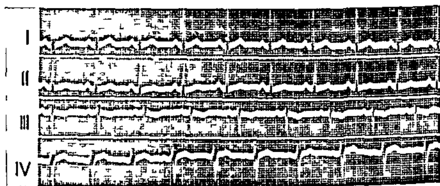
ECG 44 —Male age 25 diabetic coma *First record half year before profound coma* Sinus bradycardia rate 55 QRS_1 of low voltage as may be seen in a vertically placed heart *Second record during coma* RT_1 and RT_3 now slightly depressed QRS_4 polyphasic T_1 isoelectric T_2 and T_3 diphasic and T_4 semi inverted changes indicate myocardial involvement probably due to changes in hydrogen ion concentration



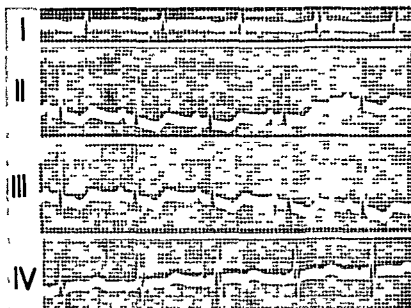
ECG 45 —Male age 9 acute rheumatic carditis *Record A* Sinus tachycardia of 115 QRS_1 notched T_1 low abnormalities indicate myocardial involvement *Record B* QRS_1 and QRS_2 of higher voltage P R interval measures 0 20 to 0 22 seconds indicating involvement of conduction system



ECG 17 —Male age 23 Recurrent rheumatic carditis with appearance of pericarditis in the second week *1st week* ECG essentially normal *2nd to 4th week* Gradual inversions of T_1 T_2 and T_4 later gradual regression of T wave inversions Changes compatible with diagnosis



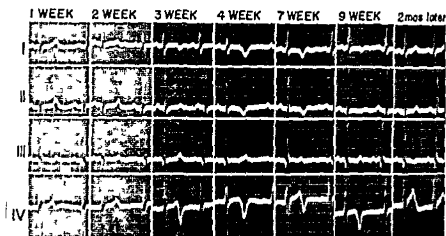
ECG 18 —Female age 38 moderate hypertension Left axis deviation of normal degree



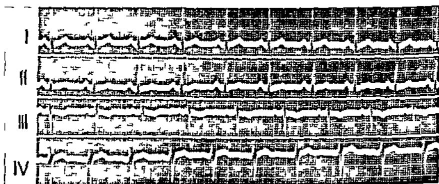
ECG 48 —Female age 29 alkalosis due to pyloric obstruction R T and R T_3 depressed T_1 iso electric T and T_4 inverted Changes indicate myocardial involvement due to changes in hydrogen ion concentration of the blood



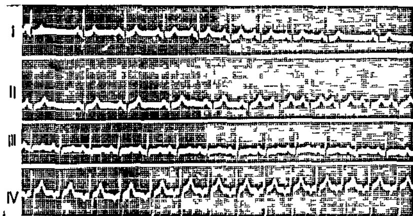
ECG 49 —Male age 32 T_2 and T_3 are inverted as occasionally may be seen in normal individuals



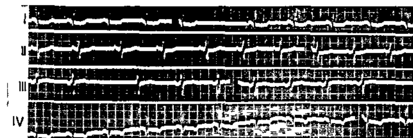
ECG 17.—Male, age 23. Recurrent rheumatic carditis with appearance of pericarditis in the second week. *1st week.* ECG essentially normal. *2nd to 4th week.* Gradual inversions of T_1, T_2 and T_4; later gradual regression of T wave inversions. Changes compatible with diagnosis.



ECG 18.—Female, age 38, moderate hypertension. Left axis deviation of normal degree.



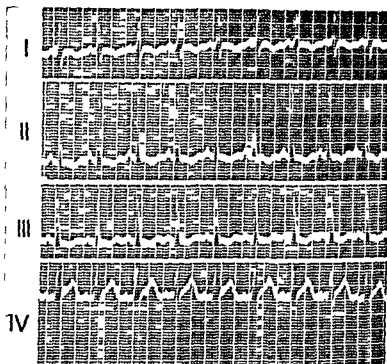
ECG 52.—Male, age 21, chronic rheumatic mitral defect, moderate stenosis and insufficiency. Marked sinus arrhythmia, no evidence of myocardial involvement.



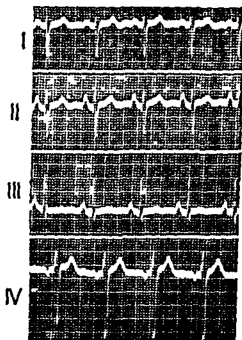
ECG 53.—Male, age 76, brain tumor. Regular sinus rhythm with periods of sinus arrest, small Q_1 and Q_4 present, left axis deviation. R T_1 and R T_2 depressed, R T_3 slightly depressed, T_1 diphasic, T_2 low, T_4 inverted. Changes indicate myocardial damage since no digitalis has been given.



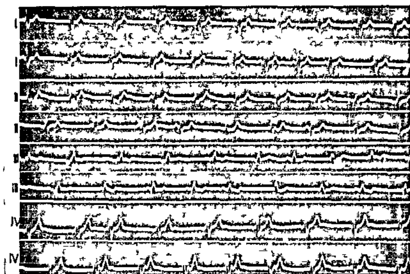
ECG 54.—Female, age 66, coronary artery disease. Regular sinus rhythm with frequent auricular premature beats occasionally forming trigeminal rhythm, left axis deviation. R T_1 and R T_2 slightly depressed, T_1 low, T_4 semi-inverted. R-T and T wave changes indicate myocardial damage since no digitalis had been given.



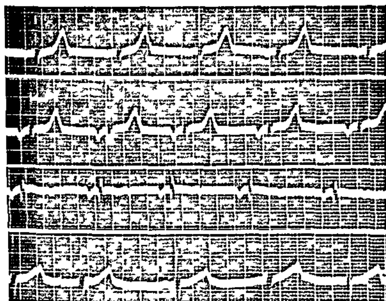
ECG 21.—Male, age 41, malignant hypertension. Sinus tachycardia of 115, tendency to right axis deviation, T wave inversions in standard leads. Changes interpreted as evidences of myocardial damage.



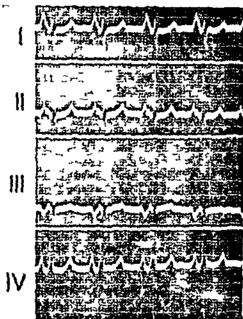
ECG 22.—Male, age 42, chronic cor pulmonale due to chronic bronchiectasis. Prominent P waves and marked right axis deviation. Changes are evidences of increased right ventric[illegible] work.



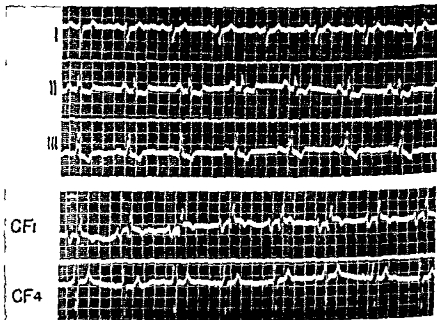
ECG 57 —Male age 74 same patient as ECG 56 Continuous strips of all four leads interpretations the same



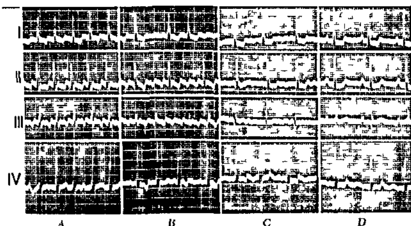
ECG 58 —Male age 8 chorea P_1 iso electric P_2 and P_3 inverted ectopic pacemaker *probably auricular Changes have no clinical significance* No further abnormalities present



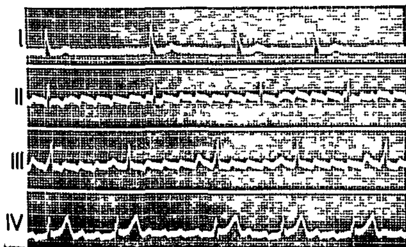
ECG 25.—Female age 18 mitral stenosis and insufficiency ECG reveals right axis deviation and marked prominence and widening of P_1 and P_2 Changes usually seen in mitral stenosis



ECG 26.—Male age 23 mitral and tricuspid disease Regular sinus rhythm P waves notched and widened P R measures 0 22 seconds right axis deviation R T_2 slightly depressed T_2 diphasic T_3 inverted The RAD and the R T and T wave changes are evidences of increased right ventricular work P wave changes may be seen in rheumatic heart disease No digitalis

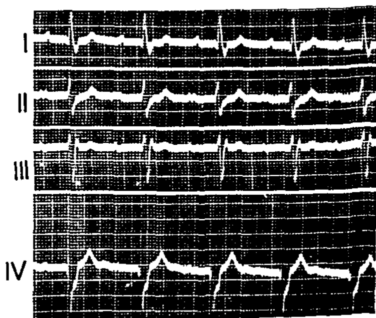


ECG 61 —Male age 61 essential hypertension paroxysmal auricular flutter for past 10 years *Record A* Auricular flutter with 2 1 ratio present *Record B* Two days later after 1 5 gm digitalis irregular ventricular response now present *Record C* Three days later after 2 8 gm digitalis auricular fibrillation now present R T_1 R T and R T_4 slightly depressed T_1 and T_4 diphasic digitalis stopped *Record D* Next day regular sinus rhythm R T_1 R T and R T_4 more depressed T_1 T_2 and T_4 diphasic R T and T wave changes suggest digitalis effects



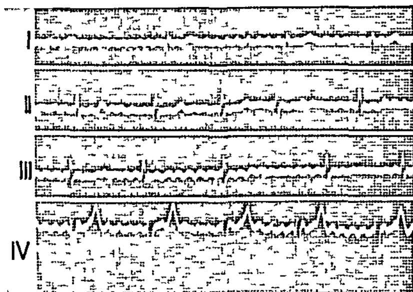
ECG 62 —Male age 62 auricular flutter for three years consistently refractory to medication Irregular AV ratio of 4 1 to 6 1 QRS_1 slurred QRS_4 shows qualitative changes but insufficient for diagnosis of myocardial damage

ECG 29 —Male age 26 mıtral stenosıs and ınsufficıency rheumatıc actıvıty P waves widened P R interval prolonged to 0 28 seconds as seen ın acute rheumatıc cardıtıs

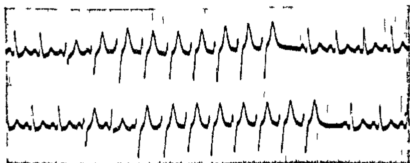


ECG 30 —Male age 67 coronary artery dısease P R 0 28 to 0 36 seconds ınterventrıcular conductıon defect ıs present QRS measures 0 16 seconds Chan,es ındıcate myocardıal damage but have not altered ın two years

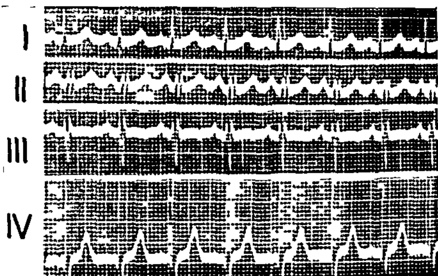
ventricular beat R T segments depressed in all four leads T waves diphasic in all four leads R T and T wave changes indicate acute coronary insufficiency frequently seen in rapid tachycardia The completely irregular spacing of the ventricular complexes establishes the diagnosis of auricular fibrillation



ECG 65 —Male age 34 chronic rheumatic valvular [illegible] mitral stenosis and insufficiency Auricular fibrillation with well controlled ventricular rate well defined fibrillatory waves



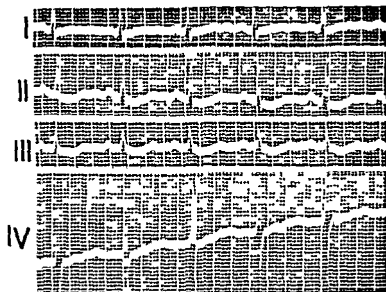
ECG 66 —Male age 54 angina pectoris Lead 2 illustrated in continuous strip marked R T segment depression immediately after exercise three minutes thereafter short runs of ventricular tachycardia Patient reported that moderate exertion frequently brought out rapid palpitation



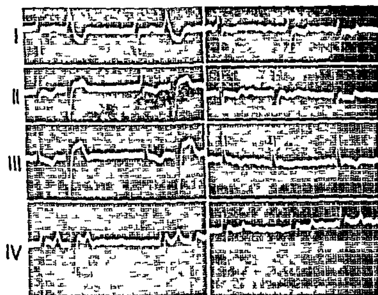
ECG 34 —Male age 73 QRS M shaped Finding abnormal although insufficient to diagnose myocardial damage



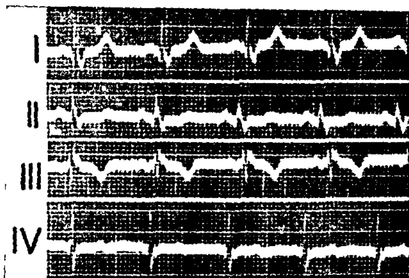
ECG 35 —Male age 68 coronary artery disease QRS complexes are of very low voltage Changes indicate myocardial damage



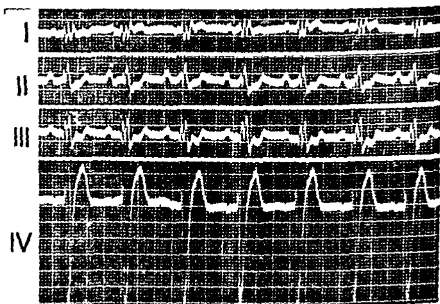
ECG 69 —Male age 53 chronic rheumatic valvular disease mitral stenosis and insufficiency digitalis 0 1 gm daily for past 3 years Regular sinus rhythm R T_2 and R T_3 depres ed R T_4 slightly depressed T_1 low



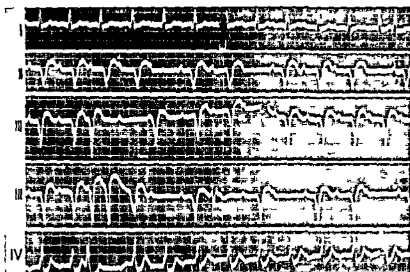
ECG 70 —Female age 28 chronic rheumatic valvular defect with long standing backward failure digitalis 0 45 gm daily for four weeks prior to first ECG *First Record* Auricular fibrillation with high degree of AV dissociation frequent ventricular premature beats form



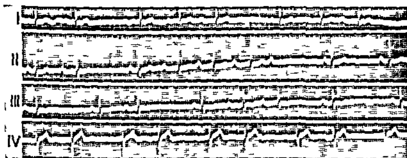
ECG 38.—Female, age 53, essential hypertension. QRS slurred, notched and widened in its thickest portion (S_1), measures 0.12 to 0.14 second. T_3 deeply inverted, T_4 low. Changes usually indicate myocardial damage with atypical right bundle branch block. Pattern occasionally seen in completely normal individuals.



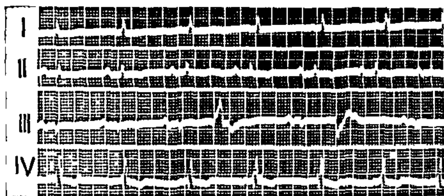
ECG 39.—Female, age 43, coronary artery disease, essential hypertension. QRS complexes are M-shaped in the standard leads. QRS widened to 0.14 to 0.16 second. R T_2 and R T_3 slightly depressed. T_1 low, T_2 and T_3 diphasic. Changes indicate myocardial damage.



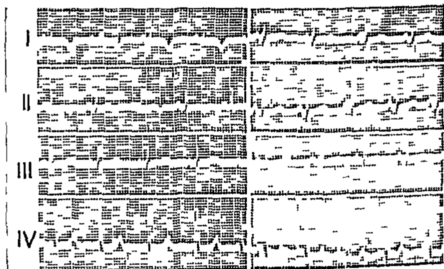
ECG 72 —Male age 82 coronary artery disease fracture of femur prophylactic digitalization to point of intoxication First and second degree heart block with Wenckebach periods P R_1 prolonged to 0 28 sec occasional auricular and ventricular premature beats Lead 2 Wenckebach periods with varying AV ratio present (5 4 3 2 4 3) Lead 3 Wenckebach periods with bizarrely spaced ventricular premature beats Left axis deviation QRS slurred notched and widened to 0 16 sec R T_1 slightly depressed R T_4 markedly depressed R T_2 and R T_3 elevated T_1 low T_4 diphasic Left bundle branch block with first and second degree heart block after digitalis



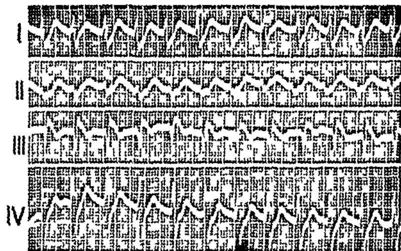
ECG 73 —Female age 30 attempted suicide with 150 grains of digitalis Wenckebach period with occasional sino-auricular ventricular block (second period of Lead 2)



ECG 42 —Male age 64 coronary artery disease Regular sinus rhythm occasional ventricular premature beats T waves low or semi inverted in all leads QRS of low voltage Changes indicate myocardial damage since no digitalis has been given



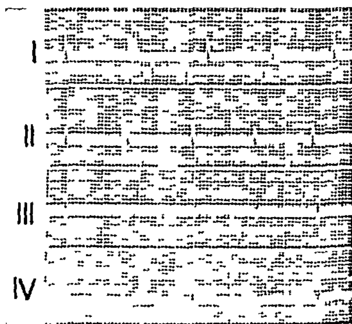
ECG 43 —Male age 6 acute glomerulonephritis *First record* Regular sinus rhythm T_1 and T_2 deeply inverted changes indicate myocardial involvement *Second record* one month later Essentially normal



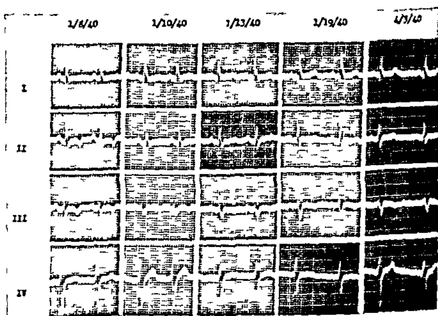
ECG 76.—Male, age 74; development of supraventricular tachycardia after operation. QRS complexes previously of normal configuration; quinidine sulfate 0.2 gm. given every 3 hours without effect on ectopic pacemaker. After quinidine, QRS complexes widened to 0.14 to 0.16 seconds as toxic effect on interventricular conduction system.



ECG 77.—Male, age 62; coronary artery disease and 2:1 heart block. Right axis deviation. QRS slurred, notched and widened to 0.14 to 0.16 sec. R T_3 depressed, T_3 diphasic, T_4 semi-inverted. High voltage QRS suggests right bundle branch block; auriculoventricular heart block indicates definite involvement of conduction system.



ECG 46—Female age 30 generalized edema due to nephrosis with pericardial effusion QRS moderately low voltage T waves iso-electric Changes suggest a pericardial effusion



ECG 47—Female age 42 trichinosis with myocarditis *Record 1/8/40* T_1 iso electric T_2 and T_3 inverted *Record 1/10/40* T waves low in standard leads *Records 1/13/40* and *1/19/40* T waves greater in standard leads and iso electric in precordial leads *Follow-up record 4/3/40* Essentially normal

CHAPTER 36

METHODS OF TREATMENT OF DISTURBANCES OF THE CIRCULATORY SYSTEM

CIRCULATORY disturbances may be treated by diet physical methods injection and aspiration the administration of drugs surgery occupational therapy and spa therapy (p 3765)

DIET

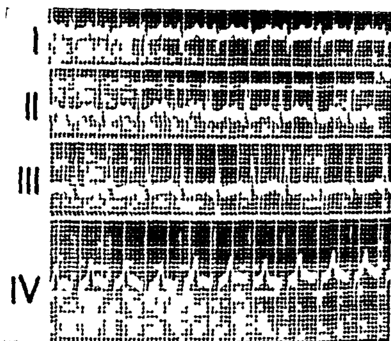
The *low calory diet* (p 669) is particularly useful in the treatment of hypertension (p 900) in the obese In the management of edema in backward failure (p 941) the practitioner may try the low calory destricted fluid regime of Karell (p 670) or a low sodium diet (p 682) and unlimited fluids

PHYSICAL THERAPY

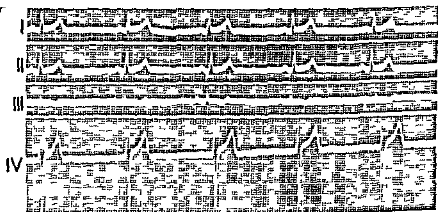
Physical therapy is of considerable value in different types of circulatory disturbance *Exercises* are advisable for the protection of cardiac reserve and in rehabilitation after prolonged periods of bed rest such as follow myocardial infarction *Vasculators* are enthusiastically advocated by many who have large experience in the treatment of peripheral vascular disease *Vagal pressure* is employed for its cardio inhibitor effect in paroxysmal cardiac irregularities

Vagal Pressure —The vagus may be stimulated by direct pressure using the thumb pressed into the carotid sheath in the neck or by compression on both eyeballs When these maneuvers are successfully employed they restore sinus rhythm in the presence of a paroxysmal cardiac irregularity The therapeutic endeavor is not without danger however since there may be syncope and temporary cardiac standstill as the result of over enthusiastic compression During the vagal pressure the examiner should apply pressure with one hand and with the other hand hold the stethoscope at the cardiac apex Pressure is discontinued instantly that sinus rhythm is restored or an abnormal bradycardia is noted

A safer but more uncomfortable method of vagal stimulation is through the induction of emesis by teaspoonful doses of ipecac (p 1757)



ECG 50 —Female age 12 periarteritis nodosa Sinus tachycardia of 210 no evidence of myocardial damage



ECG 51 —Male age 37 duodenal ulcer Sinus bradycardia of 47 no evidence of myocardial damage

If the patient is unconscious or under the influence of narcotics the pain from the insertion of the large needle is not particularly noted Otherwise a subcutaneous and intradermal injection of 1 per cent procaine is advisable

When venous pressure is high in cardiac failure the vessels are distended and penetration of the vein is simple The blood pressure cuff is employed as a tourniquet It is inflated to a point midway between systolic and diastolic pressures The needle is inserted into the vein Obturator and stylet are removed and the blood is collected in a large container The blood pressure cuff is not deflated until the bleeding is completed At least 500 cc of blood should be removed In plethoric cyanosed cardiac patients there need be no hesitancy in removing considerably more than 500 cc of blood provided symptoms of circulatory collapse are not experienced

Phlebotomy from healthy donors for transfusion purposes should not exceed 500 cc The donor should have had a serologic test for syphilis within a few days before the transfusion and he should fast from eight to twelve hours before the bleeding Vacuum collection flasks facilitate the blood letting

PARAVERTEBRAL NERVE BLOCK

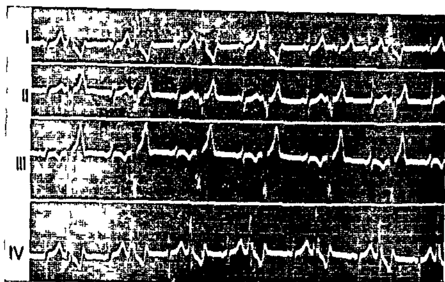
Paravertebral nerve block has become valuable for the treatment of various conditions such as *intractable visceral pain certain neuralgias vasospasm* of the extremities *intermittent claudication excessive sweating* of the extremities and to stimulate collateral circulation after *obstruction of an artery*

For the practicing physician the most important application of this method of treatment is the injection in the upper thoracic region for intractable *status anginosus* (p 891) The procedure should be carried out with the patient in bed

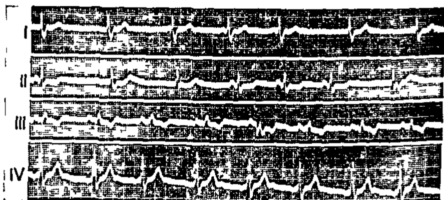
In the upper thoracic region the points of injection are 3 to 4 cm lateral to each spinous process This is the level of the transverse process or rib of the lower vertebra Needles are inserted through the sterilized skin perpendicular to the surface of the back At a depth of 2 to 5 cm the rib or transverse process is met following which the needle is inserted slightly caudad and at a 20 degree angle toward the mid line Bone is again felt at a depth of 3 cm below that of the rib This bone is the lateral aspect of the vertebra After aspiration 1 cc of 2 per cent procaine is injected into each needle In 15 minutes the arm the side of the neck and head may become hot and the Horner s syndrome develop There may be intercostal nerve anesthesia especially in the lower dorsal region If these signs develop satisfactorily 2 to 3 cc of 1 per cent procaine are injected into each needle followed by 5 cc of 95 per cent alcohol Each injection should be preceded by aspiration in order to make sure that the needle point is not in the subarachnoid space or in a blood vessel The patient is kept quiet in bed for twenty four hours permitted to be in a chair the following day and is allowed to be up on the third day

One of the most troublesome *complications* of the therapeutic block is causalgia Other complications are pneumothorax and pleuritic pain

If after the first procaine injected the desired result is not obtained the needles may be readjusted and a second attempt made Rather than



ECG 55.—Female, age 7½, no cardiac abnormality. Regular sinus rhythm with frequent premature beats forming bigeminal rhythm.



ECG 56.—Male, age 74, chronic bronchitis with emphysema and coronary artery disease. Wandering pacemaker. P wave changes its relation to QRS complex. QRS slurred, notched and widened in its 2nd portion to 0.14 sec. R T_2 and R T_3 slightly depressed. T_3 inverted. QRS and T wave changes indicate myocardial damage with right bundle branch block.

As an alternate to the powdered leaf of digitalis we favor the use of *digoxin* derived from *digitalis lanata* This product is marketed in tablets containing 0 25 mg (1/240 gr) and in 1 cc ampoules for intravenous use The latter contain 0.5 mg (1/120 gr) of the drug which must be diluted before use to 10 cc with saline

Official N N.R preparations of digitalis each of which has its advocates include digalen digifolin digilanid digipoten digitalin (German) digitaline nativelle digitan digital gitalin (amorphous) ouabain (g strophanthin) scillaren B scillaren urginin and strophanthin

Bioassay of Digitalis—Powdered digitalis leaf varies in potency depending on the locale in which it is grown and the method of manufacture In order to insure a reasonable measure of the potency of different preparations the drug is standardized biologically

The official method of standardization (U S P XII) is the cat method of Hatcher and Brody This method is based on the finding that the minimal lethal dose of ouabain for cats is 0 1 mg per kilogram A given amount of an unknown digitalis preparation is injected intravenously and then ouabain is given slowly until death occurs The difference between the theoretical lethal dose of ouabain and the actual amount used is a measure of the potency of the digitalis in terms of *ouabain* One cat unit (0 08 gm) represents the amount of digitalis which is lethal to 1 Kg of cat

Since bioassays are subject to considerable variation it is a safe procedure for the clinician to limit himself to the use of one preparation From a practical standpoint assay is only a guide to dosage which is in actuality determined by the condition of the patient Purified cardiac glucosides need not be assayed but may be administered by weight

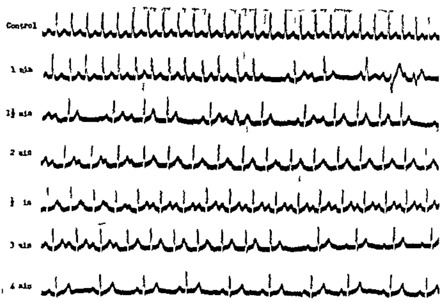
Absorption and Excretion—Digitalis is slowly and incompletely absorbed from the small intestine However absorption is sufficiently uniform for the reliable use of the oral route in the accurate administration of the drug Absorption also occurs in the large bowel allowing for rectal administration in patients suffering from persistent emesis Strophanthus and squill are absorbed slowly and irregularly when given by mouth and cannot be relied upon by this route

Digitalis should be given with meals to minimize the local irritant action which often causes *nausea* and *vomiting* Absorption of an oral dose is completed within two hours and the full cardiac effect appears within six hours

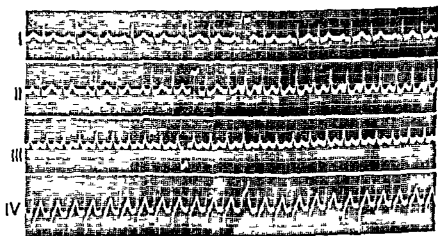
Since digitalis is only partially absorbed from the intestinal tract the same cardiac effects are obtained with smaller parenteral doses of the cardiac glucosides within fifteen minutes after intravenous injection The cardiac glucosides retain the local irritant action of the crude drugs and may cause pain and sterile abscess formation after subcutaneous and intramuscular injection

The excretion of digitalis is slow Accordingly cumulative poisoning is commonly encountered The cardiac action persists for several weeks after the drug has been stopped This necessitates the careful determination of the time and degree of previous dosage before starting digitalis anew

The amount of digitalis excreted each day is not constant As the drug accumulates in the body the rate of excretion increases until a definite



ECG 59—Male age 31 supraventricular tachycardia postoperatively with rate of 200 Subcutaneous injection of 20 mg of *mecholyl* Two continuous strips
One minute after injection sinus beats appear with varying degrees of AV and interventricular conduction delays two minutes after sinus tachycardia of 120 is present, P R prolonged to 0 28 sec two and a half and three minutes after P R interval constantly changing four minutes after regular sinus rhythm



ECG 60—Male age 54 paroxysm of supraventricular tachycardia while electrocardiogram is taken Lead 1 regular sinus rhythm with frequent auricular premature beats Lead 2 unchanged in first portion but onset of supraventricular tachycardia in second half, Leads 3 and 4 supraventricular tachycardia with rate of 210

2 *Conduction* between auricles and ventricles is definitely slowed and impaired This is a therapeutic effect when the ventricular rate is excessively rapid It is toxic when partial or complete heart block is produced
3 The *tonicity* of heart muscle is increased This constitutes a favor able effect in cardiac failure with impairment of this property but a toxic effect in the presence of isotonicity (p 772)
4 *Contractility* is increased again a favorable effect in heart failure but an unfavorable manifestation in the normal subject
5 *Irritability* of cardiac muscle is increased an unfavorable effect at all times since ectopic foci may arise and assume the functions of the pacemaker

The sum of these actions *in the normal heart* is a diminished cardiac output a diminished cardiac rate a fall in minute output impairment of mechanical efficiency and an over all toxic effect

The same actions *in the decompensated heart* increase systolic dis charge and cardiac output limit the diastolic overdistention slow the excessively rapid rate diminish the hyperirritability and excitability of the ventricular muscles and make for greater efficiency of pump activity

Extracardiac Actions—Digitalis increases tissue resorption of oxygen from the peripheral blood Flight surgeons have noticed increased anox emia tolerance after digitalization

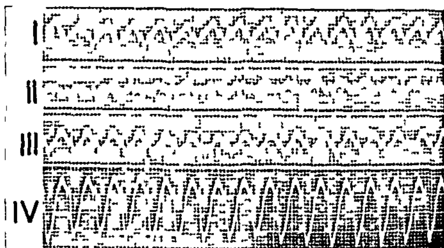
The *other extracardiac activities of digitalis are for the most part* toxic Large doses produce a generalized *vasoconstriction* by a direct ac tion thus limiting the use of the drug in disease of the coronary artery The powerful central stimulation of the medulla causes *nausea* and *vomit ing* which may demand discontinuance of administration Digitalis in creases the excitability of the carotid sinus in patients with the *carotid sinus syndrome* (p 912)

Digitalis is a local irritant It may produce *emesis* on contact with the gastric mucosa Hence it is best given when the stomach is full On injec tion into the local tissues it causes *pain* inflammatory responses and occa sionally a slough

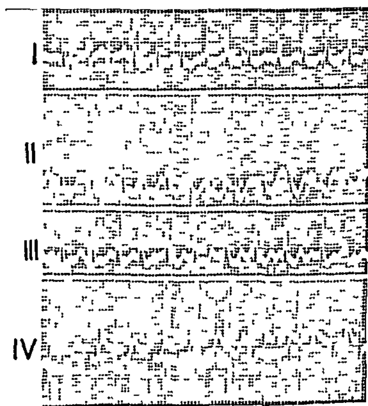
Changes in Electrocardiogram—Digitalis causes significant changes in the electrocardiogram Their recognition is important since they simulate myocardial disease The changes are due to vagal stimulation or direct myocardial action (ECG 21, 63 65, 69 70, 71 72 73 74)

The initial digitalis change in the electrocardiogram is a *depression of the RST interval* and a *decrease in the amplitude of the T wave* which may become flat and inverted In some instances the change may occur only in the RST interval in others only in the T wave If axis deviation is present digitalis changes the T wave so that it becomes opposite in direction to the QRS complex In Lead IV digitalis may cause occasional elevation of the S T interval simulating the picture of myocardial infarc tion These changes unaffected by atropine are myocardial in origin They appear two to four hours after a single massive dose and may persist for several weeks

After the appearance of T wave changes the continued use of the drug leads to various degrees of prolongation of auriculo ventricular con duction time First there is a prolongation of the P R interval which is



ECG 63 —Female age 48 chronic rheumatic valvular defect mitral stenosis and insufficiency auricular flutter for a week backward failure A 1 1 ratio ventricular rate 240 QRS complexes of low voltage in standard leads but widened to 0 12 to 0 14 sec Record could be interpreted as ventricular tachycardia except for high ventricular rate and absolute regularity



ECG 64 —Male age 59 mesenteric embolism Auricular fibrillation with very rapid ventricular rate of 210 to 240 occasional ectopic

other measures (carotid pressure eyeball pressure emetics mecholyl) fail The benefit probably is due to the vagal stimulation produced by the drug Digitalis should never be given if a *ventricular tachycardia* is present

Prophylactic Digitalization—The continuous administration of small doses of digitalis in old people with cardiac enlargement has been advocated by Christian

Dosage and Administration—More than 150 years ago Withering wrote the following classic statement regarding digitalis *Let it be continued until it acts on the kidneys the stomach the pulse or the bowels let it be stopped upon the first appearance of any of these effects*

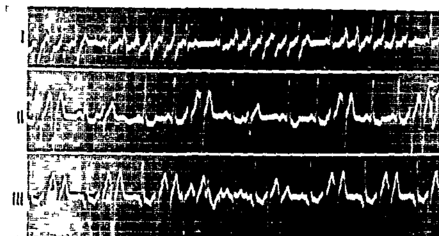
Initial Digitalization—The average patient with cardiac failure will show a full digitalis effect after 1 3 to 1 8 gm (20–27 grains) of the powdered leaf (U S P XII) have been administered in divided doses However in different patients the amount required may vary 50 per cent above and below the average Consequently it is essential to appraise carefully the clinical condition of the patient for evidences of improvement and intoxication

The rapidity with which the digitalizing dose of digitalis is administered will vary with the intensity of the cardiac indication In severely decompensated cardiac patients the digitalizing dose should be given within twenty four hours One half of the total amount (0 7 to 0 9 gm [10 to 13 grains]) should be given as the first dose and the remainder in three equal parts (0 2 to 0 3 gm [3 to 4½ grains]) Significant improvement may be apparent within six hours and the full effect is often present within twelve to eighteen hours Rapid digitalization with large doses should not be instituted if the patient has had the drug in the preceding two weeks

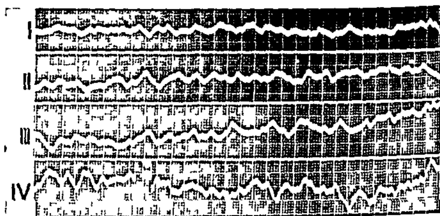
In moribund patients with congestive failure a digitalis principle should be given parenterally to secure a prompt cardiac action The proper dosage to secure full digitalization by the parenteral route is not definitely established but it is much less than the oral dose If digoxin is used the initial dose should not exceed 0 25 mg intravenously *Digoxin should never be used in a patient who has recently received digitalis since a fatality is likely to occur*

If the degree of heart failure is moderate and the patient is fairly comfortable in bed slow digitalization with smaller doses spread over a longer period is a sound procedure Digitalis leaf is given in amounts of 0 6 gm (10 gr) on the first day a similar amount on the second 0 3 gm (5 gr) on the third 0 3 gm (5 gr) on the fourth and 0 1 gm (1½ gr) on the fifth day If the patient has had digitalis within the weeks immediately preceding a smaller dose (0 1 gm three times daily) is used If the patient complains of nausea and vomiting (not due to the central action of digitalis) and cannot take the drug orally it may be administered rectally in doses of 3 to 4 cc of the tincture of digitalis dissolved in 50 to 100 cc of water every six hours

If there is no emergency and the patient is ambulatory a satisfactory schedule is to give 0 1 gm (1½ gr) of the drug three times daily with meals for one week Smaller daily amounts may be used but will result in slower digitalization It should be realized that the longer the period



ECG 67 —Male age 59 with coronary artery disease Regular sinus rhythm with frequent ventricular premature beats short runs of supraventricular tachycardia aberrant conduction of QRS_1 R T_1 R T_2 and R T_3 depressed T_1 low T_2 and T_3 diphasic R T and T changes indicate myocardial damage since no digitalis had been given the multiple ventricular and supraventricular extrasystoles indicate a high degree of myocardial irritability



ECG 68 —Male age 59 same patient as ECG 67, sudden onset of unconsciousness the next day ventricular fibrillation Patient died

other measures (carotid pressure eyeball pressure emetics mecholyl) fail The benefit probably is due to the vagal stimulation produced by the drug Digitalis should never be given if a *ventricular tachycardia* is present

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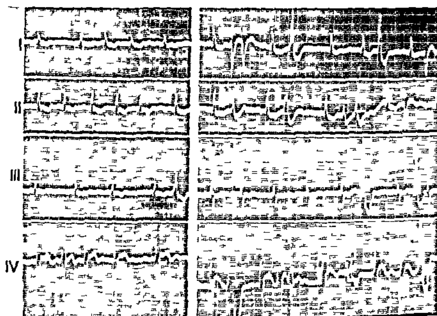
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ing bigeminal rhythm, right axis deviation R T_1 R T_2 and R T_3 depressed T_1 low, T_2 T_3 and T_4 diphasic R T and T changes probably due in part to digitalis and in part to increased ventricular work in connection with right axis deviation *Second Record* Digitalis stopped for 2 weeks auricular fibrillation with well controlled ventricular rate now present



ECG 71 —Female age 27 chronic rheumatic valvular defect with long standing backward failure *Record A* Auricular fibrillation with moderately rapid ventricular rate R T_1 and R T_2 depressed T_1 T and T_3 diphasic R T and T changes probably due to digitalis *Record B* Digitalis increased to 0 3 gm daily for two weeks auricular fibrillation still present frequent multifocal ectopic beats R T_1 R T_2 and R T_3 depressed to a greater degree than in record A bizarre periods of ectopic beats frequently seen in digitalis poisoning

in all likelihood the result of an increase in the irritability of the heart muscle

ABNORMAL RHYTHMS —Because of increased irritability of the heart muscle during digitalis therapy abnormal cardiac rhythms are prone to occur In a sense they are an aggravation of the same trend that gives rise to ectopic beats

A *ventricular tachycardia* denotes a severe grade of digitalis intoxication This should be suspected in any patient receiving the drug if a grossly irregular rate becomes regular and rapid The drug should be withheld until the exact nature of the new rhythm is determined by means of the electrocardiogram The tracing may show an *alternating* reversal in the direction of the QRS complexes This carries a grave prognosis and is usually attended by a fatal termination

Large doses of digitalis produce ventricular fibrillation *in experimental animals* It is not inconceivable that sudden death after an intravenous injection of *ouabain* or in some patients maintained on digitalis leaf may result from the occurrence of this arrhythmia

BRADYCARDIA —Depression of the sino-auricular node and the conduction system is one of the normal cardiac actions of digitalis In cases of auricular fibrillation and in heart failure with tachycardia the heart rate is slowed and approaches normal Excessive doses augment the degree of slowing and the rate may drop below 60 The bradycardia may arise from (1) *sino auricular inhibition* which in rare instances may progress to a complete auricular standstill or (2) *auriculo ventricular dissociation* Although therapeutic doses frequently cause a delay in conduction time indicated by the prolongation of the P R interval in the electrocardiogram excessive doses cause partial and even complete heart block Characteristically in digitalis complete block the ventricular rate is between 50 and 60 beats per minute and may even reach 100 Ordinarily one encounters a ventricular rate of 30 in block from other causes

In patients with *generalized edema* digitalis intoxication may occur with the onset of diuresis This is due to the fact that the edema fluid contains appreciable amounts of the drug which exert an action on the heart as fluid passes from the interstitial tissues to the plasma

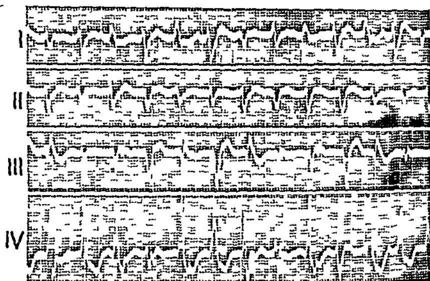
QUINIDINE

Quinidine an alkaloid of the Cinchona group was introduced in 1918 as the most effective agent for the control of *ventricular tachycardia and auricular fibrillation*

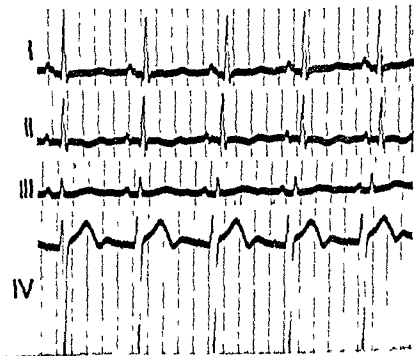
Preparations —Quinidine is available as the free alkaloid (N N R) and the official salt Quinidine Sulfate (U S P) The latter is most widely used and may be administered in the form of pills tablets capsules or cachets The usual unit dose is 0 2 to 0 3 gm (3 to 5 grains)

Absorption Fate Excretion —Like the soluble salts of its stereo-isomer quinine quinidine sulfate is absorbed readily from the gastro intestinal tract. Since it is rapidly excreted in the urine cumulative poisoning does not occur

General Pharmacology —Quinidine resembles quinine closely in pharmacological activity It is a general protoplasmic poison and has the *antimalarial action* of quinine Accordingly it may be given successfully to patients who are intolerant of the latter drug



ECG 74.—Female, age 50, coronary artery disease and digitalis intoxication from 4 gm. of drug. Ventricular tachycardia with shifting ventricular focus. An indication of a high degree of myocardial irritability.



ECG 75.—Male, age 34, frequent auricular premature beats. Quinidine sulfate (0.4 gm. [6 grains]) given every 3 hours with prolongation of Q-T interval to 0.62 seconds.

of the drug in the presence of these symptoms eventually leads to respiratory failure and collapse

Cardiovascular Accidents—Embolism has been attributed to the effect of quinidine The sudden termination of auricular fibrillation following quinidine administration is held responsible by many for the breaking off of an intra auricular thrombus from the auricular appendage

SURGERY

Major operations upon the circulatory system are rather rare but quite dramatic *Myocardiorrhaphy* involves suture of stab wounds in the heart in *pericardiolysis* the pericardium is resected *ligation of a patent ductus arteriosus* (p 958) restores normal circulatory dynamics in the face of a congenital abnormality vascularization of the pericardium is attempted in order to provide collaterals after coronary occlusion *embolectomy* such as removal of a saddle thrombus from the iliacs has occasionally been accomplished

Other operative procedures include varicocelectomy (p 3939) ligation of saphenous femoral and peripheral varicose veins incision and drainage of thrombosed lateral sinus with ligation of the jugular periarterial sympathectomy ganglionectomy and splanchnicectomy (p 914)

Surgery in the Cardiac Invalid—Surgical problems arise in the cardiac invalid just as in the more normal members of the community With procedures of *necessity* (p 3996) the practitioner has no alternative but to subject his patient to operative measures

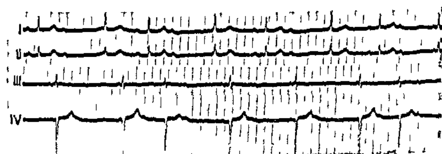
Operations of *choice* (p 3996) are deferred whenever possible if they cannot be altogether cancelled many devices are employed to assure recovery A *preoperative period of rest* for several days is recommended in an atmosphere of certainty and assurance During this stage the quality of the blood is improved if necessary by a *high protein diet* (p 674) or a *transfusion* of whole blood (p 3778) The advisability of *digitalization* (p 859) is considered and a *therapeutic test* is attempted if there is an element of doubt metabolic derangements are corrected in *diabetics* (p 1246) *hyperthyroids* (p 1197) and those suffering from *vitamin deficiency* (p 619) *sedatives* are prescribed during the day hours and *hypnotics* at night *Basal anesthesia* (p 3913) is employed if possible the operation is performed under *infiltration anesthesia* but the spinal method is avoided due to the dangers attendant upon the fall in blood pressure if an inhalation anesthetic is required the choice lies between *drop ether ethylene* and *cyclopropane* in the hands of the expert Myocardial anoxia may be prevented by the immediate postoperative use of *oxygen* an infusion of *plasma* may fortify the patient against shock The small signs of postoperative difficulties (p 4004) demand prompt attention lest major disturbances arise

The practitioner accompanies his patient to the operating room and stays with him until he has recovered from the anesthetic he makes frequent visits during the first night and the subsequent postoperative days While his vigilance has definitive positive value it has also the negative effect of preventing enthusiastic associates from excessive zeal in the administration of the alleged cardiac stimulants (p 940)

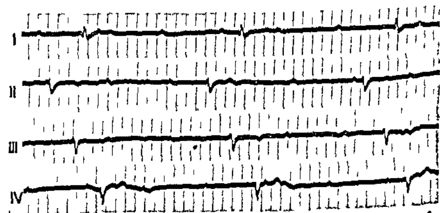
In convalescence the practitioner is confronted with much the same [illegible] presented in the patient who is recovering from an acute



ECG 78 —Male age 18 acute rheumatic carditis Wenckebach periods present mostly with 4 3 AV ratio P R interval following the dropped beat supernormally short Changes indicate involvement of conduction system



ECG 79 —Female age 29 complete AV dissociation for 10 years Discovery coincidental no previous illness probably congenital Periods of complete AV dissociation alternate with first degree heart block drugs without influence exercise temporarily reestablishes regular sinus rhythm



ECG 80 —Male age 48 coronary artery disease but no history of episodes of Morgagni Adam Stokes syndrome Complete heart block auricular rate 50 ventricular rate 18 QRS complexes widened to 0 12 to 0 14 sec

quired but it may be necessary to perform a cesarian section and the hospital stay may be prolonged to a month or six weeks

If agreement can be reached on all these points the practitioner is justified in recommending the continuation of pregnancy under the following circumstances a mild or moderate degree of *mitral stenosis* a mild or moderate *aortic insufficiency* slight *cardiac hypertrophy* slight *hypertension* or inactivity of *rheumatic fever* for a period of at least two years

SPECIAL COMPLICATIONS—The patient with a damaged circulatory system faces the following hazards in addition to those that may befall the lot of the more normal the *toxemias of pregnancy* (p 2639) are definitely more common in the woman who has precedent hypertension the extra burden may precipitate an episode of *congestive failure* (p 941) *angina pectoris* (p 890) *acute coronary insufficiency* (p 895) or *cardiac arrhythmia* (p 873) during labor *hemorrhage* is apt to be more profuse and in the puerperium there is an extra hazard of the development of *thrombosis* and *embolism*

Treatment—The pregnant cardiac is required to report to the practitioner as well as the obstetrician at very frequent intervals At first sign of difficulty she is put to bed should it become apparent before the end of the third month that difficulties are impending *interruption of the pregnancy* (p 2649) is highly advisable Thereafter it is not wise to attempt to empty the uterus until at least the seventh month when the child is viable if it is at all possible the woman should be carried further along so that there is less risk to her and her infant (p 2763)

When it becomes apparent that surgery or delivery is imminent the precautions described (p 864) are instituted If a cesarean section is performed the surgeon with written consent from patient and husband may tie off the fallopian tubes if there is agreement that another pregnancy engenders excessive hazard

OCCUPATIONS FOR THE CARDIAC INVALID

The American Heart Association has made the following suggestions for suitable occupations for those with heart disease

MEN AND BOYS SKILLED

Architecture—Draughting
Art Work—Basketry caning painting wicker furniture etc.
Automobile—Vulcanizing
Barber—Not suitable for a cardiac who cannot stand for long periods or who cannot work quickly
Book Binder—Bookbinding
Business—Fruit stand candy shop station ry (small place)
Buttons—Covering machine work
Celluloid Novelties—Engraving jigsaw and assembly This work is often done with firms making spectacles
Clerical—Bookkeeping stenography accountancy
Cobbler—Shoe repairing
Detectives—Government, public and private protection
Diamonds—Polishing
Dolls—Painting faces
Electrical Manufacture—Assembly soldering etc The cardiac who wants to be a radio operator may have to be satisfied with assembling radio parts Radio work itself is very unsuitable
File Clerk—Card indexing and filing
Fountain Pen—Grinding, rubber turning, etc. Most of this work is done while seated
Garment and Fur.—Operating finishing, etc Not suitable for neurotic cardiacs because of excessive speed.

INJECTION AND ASPIRATION

The methods of injection and aspiration that are practiced in circulatory disorders include paracentesis of the pericardium intracardiac injections phlebotomy paravertebral nerve blocks and injections of varicose veins

PARACENTESIS OF THE PLEURA OR PERICARDIUM

Aspiration of the pericardial sac is performed for the removal of excessive fluid accumulations producing compression or tamponade of the heart (p 872) Cardiac tamponade most commonly arises when the fluid accumulation is rapid The pericardial fluid may be a *clear serum* as in a rheumatic infection or it may be *bloody* resulting from trauma as in the traffic accident when the chest of the driver is jammed against his steering wheel

The most satisfactory place for pericardial aspiration is the fifth left intercostal space 1 to 2 cm mesial to the left outer border of cardiac dullness The pericardium is also approached in the epigastrium through the angle between the ensiform cartilage and the left costal border Posteriorly the site of aspiration is through the seventh or eighth intercostal space in the mid scapular line

Aspiration is made with a 17 or 18 gauge (2½ inch) needle and a large 20 or 50 cc syringe preferably one that is equipped with a two way stop cock The area should be infiltrated with procaine for local anesthesia before the insertion of the larger needle

INTRACARDIAC INJECTION

Intracardiac injection is a heroic measure reserved exclusively for attempts to restore the circulation Resuscitation may be possible within five to eight minutes after cessation of the heart beat Acute cardiac cessation is of two types (1) arrest of stimulus formation at the pace maker (2) dissolution of the cardiac cycle resulting in ventricular fibrillation

Intracardiac injection is usually made with 1 1000 epinephrine solution using an 18 gauge (2½ inch) needle If epinephrine is not available mechanical stimulation by the insertion of the needle alone may be effective The epinephrine intracardiac injection should be reserved for *sudden cardiac collapse* and *standstill* such as occasionally follow accidents in the operating room *when the patient goes into shock or expires* from the anesthesia

The site of injection should be the *right auricle* since mechanical irritation of the ventricle by needle puncture may result in an attack of fatal ventricular fibrillation A similar effect in the auricle produces auricular fibrillation which has a lesser threat to life The auricle is approached by puncture along the right border of the sternum in the third or fourth interspace The needle is directed downward and inward

PHLEBOTOMY

Phlebotomy needles are commonly 2 inches long and 13 to 15 gauge They contain both obturator and stylet Phlebotomy is indicated for *polycythemia* and for *cardiac failure* with pulmonary congestion and excessive elevation of venous pressure Repeated phlebotomies every week or so are used in the treatment of polycythemia vera depending on the blood count

CHAPTER 37

PHYSIOLOGICAL DISTURBANCES OF THE CIRCULATORY SYSTEM CARDIAC HYPERTROPHY DILATATION TAMPONADE

The majority of circulatory disturbances are dependent upon abnormalities in function Those who approach a therapeutic problem with attention focused upon morphological changes may expect to accomplish little those whose aim it is to correct a physiological disturbance have a more hopeful prospect of ameliorating the presenting complaints

The commoner pathologic physiological disturbances of the circulation are

- Hypertrophy of the Heart
- Dilatation of the Heart
- Cardiac Tamponade
- Cardiac Rate Alterations in
  - Tachycardia
  - Bradycardia
- Cardiac Arrhythmias
- Myocardial Ischemia or Anoxia
  - Angina Pectoris
  - Acute Coronary Insufficiency
  - Myocardial Insufficiency
- Vasovagal Syncope
- Carotid Sinus Syncope
- Neurocirculatory Asthenia
- Symptomatic Hypertension of the Greater Circulation
- Essential Hypertension
- Hypotension of the Greater Circulation
- Hypertension of the Lesser Circulation (Pulmonary Hypertension)
- Hypertension of the Portal Circulation
- Circulatory Failure
  - Forward Failure
  - Backward Failure (Chronic Passive Congestion)

CARDIAC HYPERTROPHY

Cardiac hypertrophy is a response of the myocardium to increased circulatory demands *In contrast to cardiac dilatation (p 870) there is* no enlargement of the cardiac chambers volume output is not decreased and congestive phenomena are not invited On the contrary the muscle mass is increased the ventricular thrust is strengthened the emptying of the chambers is completed with each systole and the stroke output may be *considerably elevated*

Etiology—Cardiac hypertrophy results from intracardiac and extracardiac causes Factors productive of cor pulmonale are discussed on p 919

make too many attempts at any one site, the needles should be withdrawn and the injection tried again at some subsequent time

For injection of the *lumbar sympathetic ganglia* exactly the same technic is used as for the thoracic The spines here are parallel to the transverse processes Therefore with the patient prone the needle is inserted 3 cm lateral to the upper level of each spine and perpendicular to the surface of the back At a depth of 4 to 5 cm the upper edge of the transverse process is felt The needle then inclines upwards and slightly inward until the side of the vertebra is felt following which the procedure is the same as outlined above

DRUGS

The Section on Pharmacology contains descriptions of those drugs which exhibit circulatory activity except for digitalis and quinidine (p 861) These two potent remedies are described in the paragraphs which follow since their therapeutic functions are preponderantly related to cardiac activity

DIGITALIS

Digitalis treatment is one of the most important and serious duties of the general physician —Wenckebach

General Introduction —The digitalis group consists of a number of drugs of plant origin whose unique cardiac actions are of great value in the treatment of congestive heart failure Although there are more than 20 crude drugs with a digitalis like action (Cushny) only a few have been adapted to clinical use The latter include *Digitalis purpurea Digitalis lanata* strophanthus and squill (*Scilla*)

The pharmacological activity of the crude drugs resides in their *active principles* which have been isolated in pure form in many instances The active principles have a similar chemical structure and are known collectively as cardiac glucosides Each is composed of a carbohydrate fraction (one to three monosaccharide molecules) and an aglycone (genin) a steroid compound possessing the phenanthrene nucleus The aglycone produces the pharmacological action of the glucoside while the sugar moiety influences its water solubility and cell penetrability The action of the *glucosides* is slower and more prolonged than that of the *aglycones*

The most widely used crude drug in the digitalis group is *Digitalis purpurea* Since its introduction by Withering in the latter part of the eighteenth century it has been subjected to extensive clinical and pharmacological study Much of the subsequent discussion of the digitalis group applies chiefly to this drug

Preparations —Despite the multiplicity of digitalis products we are convinced that the preparation of choice is the *Compressed Tablet of Digitalis Leaves* (*Purpurea*) U S P As standardized according to the U S P directions each 0 1 gm (1½ grains) is equivalent to no less than 1 0 U S P digitalis unit We do not use the official tincture or *infusion* the latter is too unstable and the tincture given in drop doses is exposed to gross error It is our opinion that every beneficial effect of digitalis can be obtained from the powdered leaf given in optimum dosage, that toxic manifestations, produced by the powdered leaf will be produced *similarly* by equivalent doses of any other of the preparations of digitalis

The increased bulk of the ventricular muscle is due to an increase in the size of the individual fiber rather than a multiplication of their numbers In contrast to dilatation the fiber is not increased in length beyond its optimum its capacity for contraction is augmented rather than lessened

Clinical Manifestations —Unaccompanied by cardiac dilatation hypertrophy of the heart causes no subjective manifestations Careful physical examination however reveals characteristic changes that are confirmed by laboratory data

In *left ventricular hypertrophy* the heart is enlarged to the left and downward (Fig 124) it assumes a triangular or boot shape the aortic knob is accentuated the aortic second sound is louder and the electrocardiogram reveals a left axis deviation followed later by increased voltage of the QRS complexes Subsequently R T_1 becomes depressed R T_3 is elevated and T_1 is inverted QRS widens and a picture of left bundle branch block emerges (ECG 1, 2, 3, 4, 18, 19, 20)

In *right ventricular hypertrophy* the waist of the heart seems to fill as the organ is enlarged to the left and upward the pulmonary artery is prominent (Fig 122) the shape of the heart is square in the anteroposterior view in the lateral view it may be seen that the retrocardiac space is filled the pulmonary second sound is accentuated the electrocardiogram reveals evidences of right axis deviation later R T and R T_3 show depression and T_2 and T_3 may become inverted Occasionally deep S T or S T_3 is observed (ECG 21, 22, 23, 24, 25 26, 27)

In contrast to the conditions that prevail in cardiac dilatation there are no demonstrable alterations in the vital capacity tests reserve is not diminished until the chambers enlarge as the result of weakening of the muscle fibers

The Athletic Heart —The practitioner hears a great deal about the athletic heart Many parents have been led to the belief that strenuous competitive exercise produces cardiac dilatation and hypertrophy they fear to permit their children to engage in healthy athletic sports and attribute any subsequent circulatory difficulty to participation in games

There is little doubt that the lay concept of the athletic heart is erroneous Circulatory disease in the athlete is dependent upon some preexistent or coexistent abnormality most likely an insidious attack of *rheumatic fever* or an unrecognized *congenital abnormality* If circulatory disease develops subsequent to vigorous athletic competition it does not differ from that which is encountered in those who have led more sedentary lives During strenuous exercise the diastolic diameter of the healthy heart is not materially increased and the systolic size is actually decreased as the result of more complete emptying The occurrence of acute dilatation due to strenuous exercise is a myth if it occurs in the athlete it is the result of some other preexistent condition

From the long range standpoint studies of crew men have not revealed any diminution in longevity nor any increase in circulatory disease compared to their non athletic classmates During active training many athletes have a marked reduction in pulse rate due to a sinus bradycardia (p 877) many noted athletes have a pulse rate that is in the forties This observation is not a cause for alarm it is not indicative of any approaching difficulty and it should not be used by insurance companies as an excuse for increasing rates

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characteristic manifestations in left and right circuits These are discussed in greater detail in subsequent paragraphs (p 941)

Diagnosis —Cardiac dilatation requires differentiation from hypertrophy of the heart and pericardial effusion In *cardiac hypertrophy* (p 867) the systolic thrust is incisive as revealed by palpation and fluoroscopic observation there are no evidences of impairment of cardiac efficiency as recorded by the various capacity tests With *pericardial effusion* (p 1008) the evidences of the systolic thrust are virtually abolished the area of dullness is triangular in form shifting dullness and flatness may be demonstrable areas of flatness due to pulmonary compression are noted posteriorly

Laboratory Aids to Diagnosis—In the asymptomatic stages of cardiac dilatation laboratory aids are of considerable value It is often possible to demonstrate a diminution in *vital capacity* (p 3739) an unsatisfactory response to *exercise tolerance tests* (p 789) an increase in the right and left heart *circulation times* (p 787) and an increase in *venous pressure* (p 784) There are no characteristic electrocardiographic changes and relatively slight alterations in blood pressure or pulse rates

Treatment —The treatment of cardiac dilatation is aimed primarily at the removal or correction of the more fundamental circulatory defect The patient with *vitamin deficiency* is given daily intravenous injections of at least 100 mg (1½ gr) of thiamine chloride (p 623) with smaller doses of niacin (p 625) and riboflavin (p 623) in the presence of *congestive failure* (p 941) a generous phlebotomy (p 852) is often desirable in *cardiac arrhythmias* (p 873) sinus rhythm may be reestablished by quinidine (p 861) or digitalis (p 854) *hyperthyroidism* yields to iodides and subtotal thyroidectomy an *essential hypertension* may be relieved by sympathectomy *anoxia* responds to oxygen inhalations (p 3827)

Digitalis Relief—Digitalis has therapeutic potentialities in cardiac dilatation Under optimum circumstances the individual fiber assumes normal length its systolic thrust is improved the cardiac chamber resumes normal size and backward pressure is reduced Clinically this is apparent from symptomatic improvement decreased circulation time lessened venous pressure and relief of distress

Digitalis Failure—Under less favorable conditions the effects of digitalization may be negligible or even noxious The burden may transcend any hope of pharmacologic improvement the myocardial fibers may be too greatly damaged to respond with a more efficient tonus the obstructive phenomena of valvular defects may not be overcome by the more powerful ventricular thrust and the damaged coronary circulation may be unable to deliver sufficient nutriment to the cardiac muscle to sustain the increased work Under these circumstances the patient is neither better nor worse and so long as there are no manifestations of toxicity the drug is continued

Digitalis Poisoning—In the least favorable examples digitalis instead of exhibiting its most powerful activity upon cardiac tonus produces changes in excitability or conductivity *premature contractions* (p 887) develop or evidences of *heart block* (p 879) are noted cardiac efficiency is definitely impaired as the result of the intended therapeutic measure and the practitioner is compelled to discontinue the drug

ceiling is reached after which the drug accumulates in the body and toxic symptoms appear

General Pharmacology—Digitalis has a complicated effect on the cardiac muscle In part the manifestations are evinced directly upon the ventricular musculature while other effects arise through vagal activity Perhaps no part of pharmacology is more perplexing to the clinician than the descriptions of the effects of digitalis on the heart and circulation.

Variable Factors in Digitalization—Digitalization is always an experiment containing several variables The responses vary with the *dose* of the drug the individual *patient-reaction* and the *state of the myocardium* at the time that the drug is administered

The variable relative to the factor of dosage is illustrated by the digitalis effect which decreases the conduction time between auricles and ventricles Under certain circumstances such as *auricular fibrillation* a desired degree of delay in conductivity is of therapeutic efficacy since it produces a slowing in the ventricular rate greater efficiency of the heart and relief of clinical symptomatology When the dose of the drug is increased beyond the optimum an *excessive conduction block* occurs the heart is inordinately slowed and therapeutic efficacy has given way to toxicology The point at which one phase gives into the other cannot be determined exactly but is dependent upon careful clinical observation and interpretation

A second variable in digitalization is the state of the cardiovascular apparatus The drug demonstrably increases the tonicity of the muscle fibers as shown by a decrease in the size of the heart during systole and diastole In the normal heart these alterations are productive of damage since cardiac filling and cardiac output are each significantly diminished A similar pharmacological effect on an overdistended heart in the presence of circulatory failure is productive of benefit Diastolic filling is more effectual the cardiac output rises ventricular emptying is complete and venous pressure falls Thus qualitatively similar pharmacological actions may produce effects that are beneficial or harmful In predicating the response there is no rule of thumb to guide the clinician and he must rely upon clinical observation and interpretation

Finally to add to the difficulty *individual patients exhibit varying responses* The function of contractility may respond sensitively in one patient whereas conductivity is earliest and most strikingly affected in another Thus a dose of digitalis administered in the hope of causing a reduction in cardiac size may actually produce a conduction block or some type of cardiac irregularity

Superimposed on all other burdens, the clinician has no way of accurately determining the degree and amount of absorption and excretion of the drug The only possible method of mastering the intelligent use of digitalis is to become thoroughly familiar with the pharmacologic and toxic potentialities and attempt to interpret the reaction of the patient in terms of these variables

Cardiac Effects—Digitalis produces the following effects upon the heart itself

1 The *pacemaker* is not significantly or consistently affected one way or another

CHAPTER 38

PHYSIOLOGICAL DISTURBANCES OF THE CIRCULATORY SYSTEM. DISTURBANCES IN CARDIAC RATE AND RHYTHM

CARDIAC ARRHYTHMIAS

The term "cardiac arrhythmias" is a misnomer since it includes conditions such as sinus bradycardia and tachycardia and paroxysmal auricular and ventricular tachycardia characterized by regular rhythm.

The commoner types of cardiac arrhythmia are the following:

- Disturbances Arising in the Sino-auricular Node
  - *Sinus Tachycardia*
  - Sinus Bradycardia
  - Sinus Arrhythmia
  - Sinus Premature Contraction
- Disturbances Arising in the Auriculoventricular Nodal Tissue
  - Wandering Pacemaker
  - Auriculoventricular Nodal Premature Contraction
  - Auriculoventricular Nodal Rhythm
  - Auriculoventricular Nodal Paroxysmal Tachycardia
- Conduction Disturbances
  - Sinus Arrest
  - Auriculoventricular Block
  - Intraventricular Conduction Defect (Bundle Branch Block, Arborization Block)
- Disturbances Arising in the Auricles
  - Auricular Premature Contractions
  - Paroxysmal Auricular Tachycardia
  - Paroxysmal Auricular Flutter
  - Permanent Auricular Flutter
  - Paroxysmal Auricular Fibrillation
  - Permanent Auricular Fibrillation
- Disturbances Arising in the Ventricles
  - Idioventricular Rhythm
  - Premature Contractions
  - Paroxysmal Ventricular Tachycardia
  - Ventricular Fibrillation

Etiology.—The cardiac arrhythmias arise from a variety of precipitating circumstances. It is important in each instance to elucidate the causative or provocative mechanism, especially since prognosis and therapy are often influenced more by the nature of the etiologic agent than the type of the abnormal mechanism.

The cardiac arrhythmias may be *psychogenic* in origin; they may arise from disturbances in the *involuntary nervous system*; they may follow *toxic* and *metabolic conditions*; or they may be of an *organic nature* related to pathologic lesions of the myocardium.

Psychogenic Arrhythmias.—Ventricular premature contractions, sinus tachycardia and paroxysmal auricular fibrillation are often psychogenic

usually below 0 25 second In individuals with previous disease of the conduction system higher degrees of heart block (p 879) are not uncommon. The prolongation of the P R interval is vagal to a great extent since it can be abolished by atropine

Inversion of the P wave slurring and slight notching of the QRS complex may be seen during digitalis medication

Therapeutics of Digitalis—From the discussion of the pharmacology of digitalis it must be apparent that the employment of the drug is ill advised with normal circulatory efficiency whether or not a murmur a cardiac irregularity a fever or an unusual circulatory burden is present.

The prophylactic use of the drug in an acute fever such as *pneumonia* in *rheumatic fever preceding operation following operation* or *under any unusual circumstance* can provide no benefit for circulatory efficiency and is most likely to be productive of harm The practitioner who doubts these statements need only digitalize himself under which circumstance he will find it quite impossible to carry out normal activities and will observe a measurable decrease in his urinary output

Optimum digitalis effects are observed in patients with *cardiac failure resulting from auricular fibrillation* Adequate digitalization slows the rate decreases heart size increases systolic contractility favors cardiac output ventricular emptying and mechanical efficiency of the pump provides increased cardiac rest increased diastolic filling and increased venous return with a resultant decrease in venous pressure (ECG 23)

Less striking and consistent favorable effects are noted in *congestive cardiac failure with sinus rhythm* Only a small proportion of the patients is favorably influenced an equal number suffers from toxic effects while the largest group does not seem appreciably affected one way or the other

Digitalis effects are not dependent on the etiology of the cardiac disturbance The remedy works best in the presence of inactivity of the lesion as in hypertensive disorders and chronic rheumatic pancarditis It is of no avail when there has been excessive myocardial damage as in myomalacia The drug is ineffectual or even harmful in the face of active infection such as acute rheumatic fever diphtheria or syphilis and in uncorrected metabolic disorders as exemplified by avitaminosis hypothyroidism and hyperthyroidism it is dangerous when given in conditions of myocardial anoxia such as follow coronary occlusion when excessive muscle irritability may provoke the onset of ectopic rhythms Its central effect in forward failure or shock is conducive of greater rather than lesser circulatory distress

Auricular Fibrillation—Digitalis should be given to fibrillating cardiac patients only if the arrhythmia is attended by cardiac failure

Auricular Flutter—Auricular flutter with or without cardiac failure is best treated with digitalis In the first instance the mechanism of improvement is the same as is seen in auricular fibrillation with failure, in the latter the aim is to convert the flutter into fibrillation by the use of large doses When this occurs the drug is stopped and a normal sinus rhythm may be resumed If the flutter recurs or the fibrillation persists digitalis should be continued to protect the ventricles (ECG 61)

Paroxysmal Tachycardia—In some cases of paroxysmal tachycardia (usually nodal or auricular) digitalis may terminate the attack after

that the rapidity of the heart is a harmless imbalance the physician insists upon a *roentgenogram of the chest* in order to reveal evidence of tuberculous infiltration The *sedimentation rate* should be determined since any increase suggests the possible presence of a tuberculous or a rheumatic infection A *basal metabolic estimation* is performed an eleva

DIFFERENTIAL DIAGNOSIS OF

Tachycardia

Rapidity of the pulse rate is an abnormality that is much more involved than that of brady cardia It may arise from a variety of endogenous and exogenous derangements disturbing the equilibrium of the mutually antagonistic subdivisions of the involuntary nervous system the myocardium or the coronary circulation

CAUSE	DIAGNOSTIC FEATURES
Physiologic	Occurs in the newborn and in sympathicotonics (p 1395) Temporary tachycardia may be postprandial the result of overeating or follow exposure to increa ed or decreased atmospheric pressure particularly at high altitudes
Psychogenic	With excitement emotion anxiety pain or fear In neurocirculatory asthenia (p 897)
Pharmacodynamic	With sympathomimetic amines (p 3875) particularly epinephrine and amphetamine From vagal depressants particularly belladonna and atropine (p 3876) From thyroid extract and dinitrophenol (p 699)
Toxic	With nicotinism caffeinism and carbon monoxide poisoning
Infection	Particularly in tuberculosis rheumatic fever and diphtheria Get temperature chart chest x ray skin tests throat culture and sedimentation rate
Metabolic	With anoxia and hyperthyroidism B M R elevated in Graves syndrome Therapeutic test with iodine (p 1213)
Hematologic	In as ociation with hemorrhage and anemia Get hemogram and hematocrit (p 3707)
Circulatory	With forward and backward failure rheumatic *carditis myomalacia, coronary occlusion* pulmonary infarction and embolization auricular and ventricular tachycardia and auricular fibrillation Supplement physical examination with chest x ray Ecg sedimentation rate and hemogram.

tion strongly pointing to the possible presence of a hyperthyroidism (p 1197) The survey is completed by the recording of a *temperature chart* (p 3484) rectal readings being taken at four hour intervals for a period of not less than four days It is only when all of these data give normal results that the presence of a sinus tachycardia not due to organic disease can be accepted without reservation

utilized to produce full digitalization the larger the total amount of the drug required since some of the digitalis is destroyed and excreted each day

Indications to Decrease Digitalis—The basic aim of digitalis therapy in heart failure is to increase the cardiac efficiency and to remedy the abnormality in circulatory dynamics The simplest guides to the efficacy of therapy are (1) the onset of diuresis in edematous patients (2) the slowing of the pulse rate to between 60 and 70 and (3) subjective improvement In cases of auricular fibrillation the pulse deficit will decrease In the presence of manifestations of digitalization the dose of digitalis should be reduced and kept at a maintenance level In the absence of a good therapeutic result the onset of the signs and symptoms of intoxication calls for a drastic reduction in digitalis dosage and even its complete omission

Maintenance Dose—There is no fixed maintenance dose of digitalis The daily amount required to maintain the optimum cardiac effect varies from patient to patient and even in the same patient from time to time To a certain extent the size of the maintenance dose parallels the severity of the congestive heart failure In mild cases with auricular fibrillation a daily dose of 0 08 gm of powdered leaf (1 cat unit) is all that is necessary In severe cases 3 to 4 cat units (0 2 to 0 3 gm) may have to be given daily In such patients it may be impossible to avoid toxicity

Dosage in Children—Children require larger amounts of digitalis (two to five times the amount of digitalis per pound of weight) than adults

Digitalis Intoxication—The manifestations of digitalis intoxication are both subjective and objective Some patients develop only subjective symptoms and others have no discomfort but present obvious objective evidence of toxicity

Gastro intestinal Symptoms—*Anorexia nausea* and *vomiting* are among the earliest and the most common manifestations of digitalis toxicity Anorexia is usually noted first and is followed in short order by nausea and then vomiting However after large single doses vomiting may occur alone The mechanism of vomiting is still a matter of conjecture In some patients digitalis causes vomiting by direct irritation on the gastric mucosa The vomiting occurring during intoxication is produced by a systemic action of the drug either on the heart or on the medullary vomiting center There is usually a latent period of varying duration between the administration of the drug and the onset of emesis

Diarrhea may occur as the only manifestation of intoxication in patients taking large doses The exact mechanism is unknown but it is believed to be central

Cerebral Symptoms—*Headache* is a common symptom of digitalis poisoning In old patients *confusion loss of memory* and *temporary aphasia* have been observed *Excitement* and *delirium* may occur *Yellow or green vision* is an interesting but rare symptom

Cardiac Manifestations—The principal objective signs of toxicity are cardiac These often prevent the successful completion of therapy

EXTRASYSTOLES (DIGITALIS COUPLING) —Digitalis in excessive doses commonly leads to the production of auricular or more *frequently* ventricular ectopic beats These have a tendency to occur after each regular beat and give rise to *pulsus bigeminus* (digitalis coupling) The extrasystoles are

SINUS ARRHYTHMIA

In sinus arrhythmia the pulse rate waxes and wanes The variations frequently coincide with the phases of respiration though they may be independent The electrocardiographic tracings show no significant consistent abnormality in the individual cycles (ECG 52)

Pathogenesis —Sinus arrhythmia results from an imbalance in the tonus of the cardioregulator nerves (p 777) The condition is of such frequency in childhood that it is to be regarded as a normal abnormality

Clinical Manifestations —Sinus arrhythmia is *asymptomatic* unless anxiety disturbances arise as the result of heart consciousness from repeated examinations or tales of weakness of the heart

DIFFERENTIAL DIAGNOSIS OF

Bradycardia

In most instances bradycardia is a physiologic phenomenon, only rarely does it indicate cardiac or extracardiac disturbances of significance

CAUSE	DIAGNOSTIC FEATURES
Physiologic	In vagotonics and athletes in training Following prolonged febrile illnesses
Pharmacodynamic	From toxic doses of digitalis (p 860) With pilocarpine and physostigmine (p 3874)
Poisoning	In profound asphyxia particularly from over dosage of opiate (p 38.3)
Metabolic	In myxedema jaundice or uremia Get B.M.R. icterus index and blood urea
Infectious	Particularly typhoid fever (p 225) and in fectious jaundice (p 360)
With Increased Intra-cranial Tension	Particularly with abrupt elevations due to meningitis encephalitis edema or hemorrhage Look for papilledema Obtain spinal fluid with caution (p 1421)
Cardiac	With sinus bradycardia auriculoventricular nodal rhythm and heart block. Get Ecg

Treatment —Sinus arrhythmia requires only the physician s *reassurance* the child and its parents are told that the condition is neither a manifestation nor a harbinger of heart disease It needs no therapy the administration of *digitalis* is contraindicated physiologically and psychologically normal exercise is to be encouraged and athletic competition may be enjoyed so long as there are no other deterrents

SINUS PREMATURE CONTRACTIONS

See *Premature Contractions* (p 887)

WANDERING PACEMAKER

The wandering pacemaker like other nodal irregularities is of infrequent occurrence It is of greater interest to the cardiac specialist than to the practitioner The abnormality is recognizable only through electro

Quinidine possesses a more *depressant action on the myocardium* than does quinine The myocardial action of quinidine is complex and may be analyzed as follows

1 The refractory period is increased (as much as 50 to 100 per cent)
2 The excitability of auricles and ventricles is decreased
3 The conduction of impulses is slowed Large doses are apt to cause various degrees of auriculo ventricular block

Administration and Dosage —Quinidine sulfate is given orally preferably in capsules to avoid the bitter taste Idiosyncrasy is common and is detected by the administration of a small test dose (0 2 gm [3 grains])

Therapeutics *Auricular Fibrillation* —The principal indication for quinidine is auricular fibrillation without congestive failure or serious heart disease Quinidine abolishes the circus movement in the auricles by increasing the refractory period

In severe organic lesions of the heart such as *coronary artery thrombosis* or *tight mitral stenoses* the use of quinidine is dangerous The best results are obtained when the fibrillation is recent

The following dosage schedule is recommended

1 First give a test dose of 0 1 to 0 2 gm (1½ to 3 grains) for sensitivity If there is no evidence of sensitivity within four to six hours larger doses are begun
2 Doses of 0 3 gm (5 gr) are given every two hours for 5 doses
3 If toxic symptoms do not occur, the dosage is progressively increased until a result is obtained With the onset of cinchonism the drug is stopped
4 If regular rhythm is obtained dosage is decreased slowly and a maintenance dose of 0 3 gm (5 gr) is continued indefinitely Normal rhythm may result after a test dose of the drug or may fail to appear after a ten day course of the drug In the latter event the quinidine course is repeated after a preliminary period of digitalization

Ventricular Tachycardia —Large doses of quinidine are indicated in ventricular tachycardia. This arrhythmia is not uncommonly a complication of *acute coronary thrombosis* and carries a grave prognosis

Quinidine sulfate in small doses (0.2 gm [3 gr] three times daily) may be given prophylactically in cases of *coronary occlusion* to prevent the onset of ventricular tachycardia

In *paroxysmal tachycardia* (auricular and ventricular) unassociated with myocardial disease small doses of quinidine (0 2 gm [3 gr] 3 to 4 times daily) may be effective in terminating an attack

Toxicity IDIOSYNCRASY —A small dose of quinidine may cause dyspnea vertigo vomiting and diarrhea and mental depression If the annoying symptoms preclude the usual doses of quinidine potentiation with strychnine may be of practical value The simultaneous administration of strychnine sulfate 0 001 gm (grain 1/60) permits an effect with half the usual amount of quinidine

Cinchonism —Full dosage leads to cinchonism attended by tinnitus nausea vomiting, auditory and visual difficulty and delirium Continuation

AURICULOVENTRICULAR BLOCK

The degrees of auriculoventricular block may range between an increase in the conduction time to complete dissociation of auricles and ventricles

First Degree Heart Block —First degree heart block is a mere delay in conduction time (p 773) *Normally the cardiac impulse passes from auricle to ventricle in less than 0 16 second* If AV time exceeds 0 2 second it may be regarded as abnormal and there are usually deformities of the electrocardiographic complex

Pathogenesis —The main causes for delay in the AV conduction time include the administration of digitalis (p 854) degenerative heart disease associated with rheumatic *pancarditis* and coronary sclerosis (p 983) diphtheritic myocarditis (p 1013) the presence of an aortic stenosis (p 971) organic lesions of the junctional tissues (neoplasms and gummas) idiosyncrasy to morphine (p 3860) and reflex influences resulting from attacks of gallbladder colic (p 2000)

Diagnosis —The recognition of a first degree heart block is not possible from clinical evidence The electrocardiographic tracing is required for its demonstration (ECG 62, 70, 72, 73)

Treatment —The treatment of a first degree heart block is essentially directed at the elimination of the causative agency This is easily accomplished when digitalis or morphine has been administered but impossible in organic cardiac disease Under the latter condition if the patient is suffering from circulatory disturbances the effects of atropine may be noted digitalization is contraindicated

Second Degree Heart Block —With a second degree or partial heart block some of the auricular impulses are prevented from initiating ventricular contraction The blocking may occur with a regular pattern under which circumstance a ratio is established between auricular and ventricular beats the block is described as two to one three to one three to two etc Occasionally the electrocardiogram exhibits increasing degrees of delayed conduction in successive cycles until there is a complete suppression of an entire ventricular complex (Wenckebach phenomenon) (p 811)

Pathogenesis —The causes of partial heart block are those of the incomplete variety The differences are those of degree

Diagnosis —Partial heart block requires electrocardiographic investigation Only in this way is the diagnosis established with conviction (ECG 70, 72 73, 77 78)

Treatment —See *Stokes Adams Syndrome* (p 880)

Complete Heart Block (Stokes Adams Syndrome) —The third degree or complete heart block is the most important of the auriculoventricular conduction disturbances In this condition auricles and ventricles contract at independent rates the latter is said to assume the *idioventricular rhythm* which may be as slow as 15 or 20 beats to minute and occasionally rises to 40 to 50 beats to the minute

Etiology —*In complete heart block the pacemaker which assumes the* function of impulse production lies in the lower portion of the auriculoventricular node or it may be in the bundle of His Complete heart block occurs most commonly with arteriosclerotic heart disease (p 976) in digitalis poisoning (p 860) in rheumatic carditis (p 1014) and in the car

coronary closure (p 983) Too great haste in encouraging the patient to resume normal activities has obvious disadvantages, on the other hand excessive coddling results in flabbiness of the peripheral musculature and invites the development of *phlebitis* (p 1124) To prevent the latter complication early movements of the legs are encouraged and deep breathing exercises are performed as soon as comfort permits (p 4122)

Special Complications—The operative procedure may precipitate the cardiac invalid into a variety of special complications These include the development of *cardiac arrhythmia* (p 873) an attack of *angina pectoris* (p 890) *acute coronary insufficiency* (p 895) or *acute coronary closure* (p 991), episodes of *forward failure* (p 920) or of *backward failure* (p 941) *peripheral thromboses* (p 1124) and *embolizations*

The principles of management of these complications do not differ from those employed under less unusual circumstances

Prognosis—It is amazing to note the unexpectedly uneventful reactions of many profound cardiac invalids to operative procedures The united efforts of the careful practitioner the expert anesthetist and the skilled surgeon frequently provide a completely serene course in dealing with a situation packed with impending difficulties This statement must not be interpreted as an excuse for relaxation of vigilance it may give courage and solace however to the cardiac invalid who is compelled to prepare his mind for a visit to an operating theater

Obstetrics in the Cardiac Invalid—In his consideration of the advisability of impregnation in the cardiac invalid the practitioner is confronted with more than mere mechanical problems There are religious sociological and psychological aspects which require earnest attention

It is surprising to note how well the patient with a badly damaged heart goes through a period of child bearing Despite these optimistic experiences the practitioner exerts exceedingly great care to prevent the sacrifice of a maternal life in attempted pregnancy

Absolute Contraindications—Unless overruled by religious or personal scruples the practitioner is justified in advising *contraception* (p 2502) or a *therapeutic abortion* (p 2649) under the following circumstances the immediate or recent presence of an episode of *backward failure* (p 941) a permanent *cardiac arrhythmia* (p 873) *hypertension pulmonary* or *tricuspid valvular lesions* whether relative or organic (p 970) a tight *mitral stenosis* (p 970) a marked *aortic insufficiency* (p 970) evidences of *myocardial anoxia infarction* or *fibrosis* no matter how slight (p 987) recent activity of a *rheumatic pancarditis* (p 809) the suspicion of *syphilitic arterial disease* (p 1025) the presence of *subacute bacterial endocarditis* (p 1021) or manifestation of *hyperthyroidism* (p 1197)

Relative Contraindications—Under certain circumstances the patient must realize that the risk of pregnancy is excessive impregnation and the continuance of pregnancy are warranted if the woman is so situated that she can have abundant rest she must be able to enter the hospital well in advance of the date of confinement she must be freed from all duties other than those relative to her baby for a period of at least six months preferably she must be able to afford assistance in her household duties and the care of her child

Her husband should be forewarned that the expenses may be unusual Not only are the services of a trained anesthetist definitely re

monest causes for these disturbances are *coronary sclerosis* and *myocardial infarction* (p 992) the abnormality also may be produced by *digitalis* (p 860) or *quinidine* (p 861) Unusual etiologic conditions are syphilitis or diphtheritic heart disease (p 302) rheumatic fever (p 186) or cardiac failure that results from an excessively rapid cardiac action Functional blocks are rarities

Clinical Manifestations —The recognition of an intraventricular block is almost impossible without the electrocardiographic trace The striking abnormality is the deformity of *QRS complexes* with increase of *QRS time* beyond 0 10 seconds (ECG 36, 37, 72, 77) The presenting symptoms are more likely due to the *more fundamental causative agency* than to the electrocardiographic abnormality The presence of a *gallop rhythm* or *reduplication of heart sounds* suggests the asynchronism of the ventricular responses

Treatment —In bundle branch block the patient is treated for the more fundamental abnormality

AURICULAR PREMATURE CONTRACTION

See *Premature Contractions* (p 887)

PAROXYSMAL NODAL OR AURICULAR TACHYCARDIA

Supraventricular paroxysms of tachycardia may arise in the nodal tissue or the auricle an irritable focus in either area initiates impulses that *are more rapid than those of the sinus node*

Etiology —Paroxysmal nodal or auricular tachycardia is usually of functional origin it rarely occurs in patients who suffer from known organic cardiac disease The provocative factor may be *psychogenic* (p 1342) the attack may be due to the excessive use of or sensitivity to *tobacco* or *caffeine* (p 3866) it may accompany *hyperthyroidism* (p 1197) and attacks of *rheumatic fever* (p 186) *pneumonia* (p 2171) or *coronary occlusion* (p 983)

Clinical Manifestations —The paroxysm of auricular tachycardia is announced by the sudden onset of palpitation nervousness and agitation occasionally there is a feeling of faintness or actual syncope The episode may be precipitated by some type of movement or an emotional incident or it may arise without obvious cause The attack begins and ends suddenly the patient is usually aware both of onset and termination pain and precordial oppression may or may not be present

The frequency and duration of attacks vary in an unpredictable manner there may be several daily paroxysms or intervals of freedom that last for months or years the individual attack may last for a few seconds minutes hours or weeks

The presence of the condition is usually revealed by the physical examination the cardiac rate is regular and varies between *150* and *250* beats per minute there is rarely any frank evidence of heart failure but there may be dyspnea blood pressure is usually reduced in proportion to the tachycardia with prolonged attacks the slowing of blood flow may produce a peripheral thrombosis (p *945*)

Diagnosis —Auricular tachycardia requires differentiation from auricular fibrillation auricular flutter and ventricular tachycardia *Paroxysmal auric*

Instrument Making—Assembly etc Much of this work may be performed while seated

Jewelry—All processes jewelry design This work has proved to be excellent as it is light and varied

Lithography—Lettering poster artist, stone artist and photographer

Mechanical Engineering—Draughting

Photography—Retouching Darkroom conditions would not be suitable to many cardiacs Home work might be possible

Piano Actions—Gluing assembly etc

Pocket Book—Pasting and operating

Printing—Proofreading and copyholding

Salesmen—Which does not involve carrying of heavy parcels

Shoe Manufacturer—Making shoes

Steel Engraving

Tailor—Cutting fitting hand sewing machine work

Watch and Clock—Repairing The advantage of this work is that a skilled man can work at it part time in his home if necessary

MEN AND BOYS UNSKILLED AND SEMISKILLED

Apartment House—Switchboard provided the board is not too heavy and there is not too much excitement

Buildings—Elevator operators

Clerical—Filing timekeeper general office duties

Construction—Watchman provided there is not too much stair climbing

Errand Boy—Provided that heavy bundles are not carried

Hotel Clubs etc—Doorman

Janitor—Provided there is not too much heavy lifting demanded

Leather Work

News Stand—Provided there is not too much exposure to inclement weather

Packer—Packing, labeling etc Where the objects handled are small or no heavy

Restaurant—Cashier and checker

Shipping—Checker

Theatre—Ticket taker

Tobacco Companies—Stripping packing

Trunk Manufacture—Lining trays and drawers riveting small parts

WOMEN AND GIRLS SKILLED

Art Work—Fashion design painting wicker furniture etc

Basketry and Cane work

Celluloid—Painting engraving

Clerical—Bookkeeping stenography and typewriting

Clothing—Invisible mending

Clothing Manufacture—Finishing Operating is usually too strenuous The excessive speed of this industry makes it rather inadvisable

Dresses—Crochet beading Home work at this trade is sometimes suitable

Dressmaking—Hand sewing and operating

Institution—Seamstress and information clerk

Jewelry—Stringing of pearls

Laces and Fine Embroidery—Mending

Lamp Shades—Pasting or sewing

Librarian

Millinery—Millinery processes Beginners must be cautioned against errands

Office—Card index and filing

Underwear Blouses—Hand sewing Small shops where there is hand sewing and embroidery often prove good places for cardiacs

Wholesale Houses—Sample mounting

WOMEN AND GIRLS UNSKILLED AND SEMISKILLED

Apartment House—Switchboard Provided the board is not too heavy and there is not too much excitement

Buttons—Carding sorting and packing

Candy—Packing wrapping

Dolls—Packing dressing

Domestic—Matron in clubs etc

Dress Patterns—Folding wrapping etc.

Drug Samples—Filling labeling finishing etc

Gloves—Packing examining

Hair Nets—Packing examining

Hosiery—Packing examining

Hotels—Linen seamstress, kitchen work, etc

Janitress—Provided there is not too much heavy lifting demanded

Jewelry—Carding boxing

Knit Goods—Ribboning examining

Lantern Slides—Coloring

Office—Stamping labeling sorting folding posters

Packer—Buttons candy paper boxes etc Where the objects handled are small or not too heavy

Pencils—Boxing assembly

Piano Actions—Assembly etc

Ribbons—Cutting blocking finishing

Tobacco Companies—Stripping packing

Trunk Manufacture—Lining trays and drawers riveting

produce emesis this may be accomplished by injections of *apomorphine hydrochloride* (p 3854) in a dosage of 6.5 to 5 4 mg (1/10 to 1/12 gr) or the oral administration of teaspoonful doses of *Syrup of Ipecac* (p 1757) every few minutes until vomiting occurs

Mecholyl (ECG 59) —Should the various methods of vagal stimulation fail *mecholyl* (p 3874) *in a dose of 15 to 30 mg* (1/4 to 1/2 gr) *is injected* subcutaneously while the patient is recumbent The pharmacologic antidote of *atropine sulfate* 1 to 2 mg (1/60 to 1/30 gr) must be at hand to be given intravenously if necessary

Quinidine—Capsules of quinidine containing 0 2 to 0.3 gm (3 to 5 grains) of the drug are given at two hour intervals if the acute efforts to stop the attack are not successful

Digitalis—For persistent attacks digitalization is indicated since continued tachycardia with diminished blood flow may give rise to coronary insufficiency or peripheral thrombosis with gangrene of an extremity For the patient of average size 1.5 to 1 75 gm (22½ to 27 grains) of the powdered leaf (U S P XII) are given in the first twenty four hours

Prophylaxis—As a prophylactic measure between paroxysms quinidine sulfate is ordered in 0 2 to 0.3 gm (3 to 5 grains) dosage the drug is given three times daily for several days with increasingly long interruptions

PAROXYSMAL AURICULAR FLUTTER

In paroxysmal auricular flutter the rate of the upper chamber varies between 200 and 300 regular beats per minute the ventricular response is slower and may be irregular

Pathologic Physiology—The mechanism of auricular flutter depends on the *circus movement* of an ectopic impulse The latter is initiated at the entrance into the right auricle of the superior or inferior vena cava the pacemaker function of the heart is assumed by the ectopic focus which travels in a circle and the refractory period of auricular muscle is reduced so that the period of unresponsiveness is negligible The lessened ventricular response is due partly to a certain degree of conduction block and partially to the refractory period of the muscle of the ventricle

Etiology—Paroxysmal auricular flutter is rarely functional Most often it occurs in the heart that has been damaged during *rheumatic fever* (p 186) *pneumonia* (p 2171) *hyperthyroidism* (p 1197) or *acute coronary occlusion* (p 983)

Clinical Manifestations—The clinical manifestations of paroxysmal auricular flutter are similar to those of auricular tachycardia (p 881) Since the flutter is usually associated with organic heart disease there is a greater tendency to the production of *dyspnea* (p 2016) and *circulatory deficiency* (p 920) Exercise has no effect on an auricular flutter pressure on the carotid sinus slows but does not stop the arrhythmia

Complications—In a prolonged attack of auricular flutter the accompanying circulatory deficiency may give rise to backward or foreward failure and peripheral or intra auricular thromboses with local and embolic vascular phenomena

Diagnosis—The diagnosis of a paroxysmal auricular flutter may be suspected when the ventricular rate is counted at an approximate 160 per minute A definitive opinion can only be rendered after observation of

Pathology.—The average weight of the normal adult heart varies between 250 and 3 0 gm In disease the organ may weigh as much as 500 to 1000 gm The largest sizes (cor

DIFFERENTIAL DIAGNOSIS OF

Cardiac Hypertrophy

Hypertrophy of the heart may be due to any of a variety of causes which increase the work of the cardiac pump These include increased metabolic demands anatomic defects within the structure of the heart itself or increased peripheral resistance usually in the arterial bed or in the kidney

	DIAGNOSTIC FEATURES
Adhesive Pericarditis	In fixation of apex impulse (p 3548) Calcification may be demonstrable by x ray
Arteriosclerosis	In association with generalized loss of elasticity and thickening or with localized disturbances in coronary arteries aorta cerebral vessels or kidney (p 977) Note vascular changes in fundus oculi
Chronic Glomerulo-Nephritis	Elevation of systolic and diastolic pressures fixation of specific gravity of urine (p 2241) albuminuria and azotemia Note albuminuric deposits in fundus oculi
Congenital Cardiac Disease	
Coarctation of Aorta	Hypertension in both arms but neither leg (p 9 9)
Pulmonary Stenosis	With systolic murmur over pulmonary area (p 961)
Subaortic Stenosis	Harsh systolic murmur and thrill over aortic area (p 959)
Tetralogy of Fallot and Eisenmenger Complex	With cyanosis pulmonary murmur and right ventricular enlargement (p 961)
Patent Ductus Arteriosus	With continuous machinery murmur in left second interspace (p 957)
Essential Hypertension	Elevation of systolic and diastolic pressures No murmurs cardiographic urinary or fundus changes (p 900)
Hyperthyroidism	With tachycardia and elevation of B.M.R Observe therapeutic response to iodide (p 1213)
Polycystic Disease of Kidneys	With findings of glomerulonephritis and palpable masses in both loins
Valvular Defects	With aortic insufficiency and stenosis and systolic and diastolic murmurs in second right interspace (p 973) Right ventricular hypertrophy with mitral stenosis and protodiastolic murmur at apex (p 973)
von Gierke's Disease	Idiopathic dilatation and hypertrophy of the heart in glycogen disease of childhood (p. 1978)

bovinum) are seen in protracted instances of hypertensive disease (p 910) and aortic insufficiency (p 9 0)

with intermissions of several days An optimum schedule may involve the simultaneous or alternate administration of both drugs

PAROXYSMAL AURICULAR FIBRILLATION

Paroxysmal auricular fibrillation like episodes of auricular flutter are dependent upon circus movement initiated at an ectopic focus In *flutter* the circus movement is regular the auricles beat consistently and transmit a constant number of impulses to the ventricles in *fibrillation* the circus movement is irregular the impulse travels at random about the auricle and the ventricular response is entirely chaotic The fibrillating auricles undergo no effectual contraction but there are series of tiny twitching movements whose rate approximates 350 to 500 to the minute Fortunately only a fraction of these beats is transmitted across the conduction system to the ventricle a partial heart block (p 879) existing in all instances of auricular fibrillation

Etiology —Paroxysmal auricular fibrillation is most often functional it may be psychogenic (p 1342) it often complicates organic heart disease due to the rheumatic fever or coronary sclerosis it may be produced by excessive use or sensitivity to alcohol (p 3847) tobacco (p 3884) or caffeine (p 3866) it occurs frequently in hyperthyroidism particularly in the immediate postoperative period (p 1215) and it may also accompany other surgical procedures such as those involving the gallbladder and the biliary passages (p 1091) Recent myocardial infarction due to coronary closure often precipitates episodes of fibrillation

Clinical Manifestations —The clinical manifestations of paroxysmal auricular fibrillation resemble those of auricular tachycardia (p 882) The patient is usually acutely aware of the onset and termination of the attack which is accompanied by nervousness palpitation weakness fainting and fluttering sensations in the precordial region The ventricular rate is totally irregular and varies between 120 and 170 beats per minute There is often a clearcut *pulse deficit* due to a disparity between apical and radial counts Symptoms of *coronary insufficiency* an *angina* or *forward failure* may be encountered

Diagnosis —The diagnosis of a paroxysm of auricular fibrillation rarely offers difficulties the pulse rate and the cardiac sounds are irregularly irregular the electrocardiographic tracing reveals absence of the P waves there is no regular pattern for the ventricular responses (ECG 23, 61, 64, 65 70 71)

See *Differential Diagnosis of Paroxysmal Tachycardia* (p 882)

Treatment.—The treatment of paroxysmal auricular fibrillation follows the methods employed in attempt to relieve paroxysmal auricular tachycardia (p 882) Main reliance is placed upon *sedation* (p 3837) *vagal pressure* (p 851) and oral doses of *quinidine* (p 862) The use of alcohol caffeine and tobacco is interdicted hyperthyroidism is controlled by the administration of iodides preparatory to surgical interference (p 1214) myocardial ischemia and anoxemia are best controlled by inhalations of oxygen

The use of *digitalis* is avoided in paroxysmal auricular fibrillation since the drug tends to perpetuate the abnormality If the attack persists however and there are clearcut evidences of circulatory deficiency

Pathology —The average weight of the normal adult heart varies between ° 0 and 350 gm In disease the organ may weigh as much as 500 to 1000 gm The lar est sizes (cor

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Hypertrophy of the heart may be due to any of a variety of causes which increase the work of the cardiac pump These include increased metabolic demands anatomic defects within the structure of the heart itself or increased peripheral resistance usually in the arterial bed or in the kidney

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beats to the minute The ventricular complexes usually have a markedly abnormal appearance on electrocardiography Normal ventricular complexes accompany only those idioventricular rhythms that initiate in the bundle of His The auricles may show any type of rhythm including the sinus variety nodal rhythm or one of the types of circus movement such as fibrillation or flutter

Idioventricular rhythm indicates serious cardiac damage unless it is due to overdigitalization Treatment is directed toward relief of the conduction defect and if the latter is complete and irrevocable digitalization is advisable

PREMATURE CONTRACTIONS (EXTRASYSTOLES MISSED BEATS DROPPED BEATS)

Ventricular premature contractions are most frequently observed but extra beats may also arise in the sinus node (p 877) or the auricles (p 878) The origin of the ectopic beat is clarified by electrocardiography which recognizes ventricular sinus and auricular premature contractions

Electrocardiographic Appearance.—In a *sinus premature contraction* the irregular beat resembles the normal cycle except that the time interval is decreased in an *auricular premature contraction* an abnormal P wave is followed by the normal or usual ventricular complex and there is a very short compensatory pause *nodal premature contractions* are those in which the P wave bears no fixed relation to the QRS the *ventricular premature beats* which are most frequently observed have no precedent P the QRS complex is bizarre and it is usually followed by a *compensatory pause*

Bigeminy and Trigeminy—If the ventricular premature contraction follows each normal systole the rhythm is described as *bigeminal* if the extrasystole follows each second normal beat, the condition of *trigeminy* exists (ECG 54, 60, 67, 70, 71, 72, 75)

Etiology—Premature contractions are more often observed in the normal than the damaged heart They occur at any age and are most frequently seen in childhood and adolescence Occasionally they are induced by psychic strain or by drugs, particularly digitalis caffeine nicotine coffee tea and alcohol They are encountered in the postinfectious states and may be precipitated by change of position such as lying on one side or another

We have the impression that premature contractions occur almost universally but that their presence is not registered by the well integrated individual The condition is drawn to the practitioner s attention most often by the sensitized the neurotic and those who are heart conscious

Clinical Manifestations—It is our opinion that premature contractions most often are asymptomatic When their presence becomes known to the patient the presenting manifestation is a feeling of irregularity a precordial bumping a sensation that the heart has stopped or a complaint of choking Those with an anxiety neurosis (p 1347) immediately develop an aura of associated complaints they note cold hands and feet which they interpret as bad circulation gasping respiration pavor nocturnus (p 1341) insomnia and fear of impending dissolution

Diagnosis—The diagnosis of a premature contraction is usually obvious from physical examination The practitioner may note an irregularity

Diagnosis —Cardiac hypertrophy requires differentiation from *dilatation* and *pericardial effusion* (p 1008) The criteria are discussed in the section on Cardiac Dilatation (p 871)

Treatment —Since cardiac hypertrophy represents an adequate response to increased circulatory demands therapy is directed at the elimination of the more fundamental defect In contrast to the circumstances that prevail in dilatation *digitalization can only do harm* and the use of the drug is strictly contraindicated

The most satisfactory results of therapy in conditions of cardiac hypertrophy (p 867) are observed when a *hyperthyroidism* is corrected by subtotal thyroidectomy (p 1214), less obvious benefits are occasionally encountered in the operative treatment of *hypertension* (p 914), little or nothing can be expected when the hypertrophy is of intracardiac origin

CARDIAC DILATATION

Confronted with excessive mechanical strain in the nature of an augmented venous inflow or undue elevation of arterial pressure the normal heart manifests remarkable reserve power In the experimental animal for example increases in venous inflow of several hundred per cent are handled with such efficiency that only slight elevation of venous pressure and minimum distention of the cardiac cavities are demonstrable

There is a point however at which the capacity of the normal heart becomes exceeded by the demands Reserve power is lessened the heart responds by lengthening the individual muscle fiber beyond its optimum distention of the cardiac cavities failure to eject as much blood as is received increase in venous pressure and the eventual development of backward failure (p 941)

Etiology —Cardiac dilatation results from the same factors that produce hypertrophy (p 867) When the compensatory mechanisms of the heart are no longer adequate the individual fibers are stretched beyond their optimum the capacity of the cardiac chambers is increased and circulatory failure impends

Clinical Manifestations —In the vast majority of instances cardiac dilatation is an *asymptomatic disorder* due to the amazing reserve power of the organ The dilated heart is capable of maintaining an efficient circulation for ordinary needs it may even respond to slightly excessive demands

The careful clinician is often enabled to diagnose cardiac dilatation long before subjective distress is observed In the presence of *left ventricular hypertrophy* (p 869) he notes that there is less accentuation of the second sound, the murmur of a relative mitral insufficiency may be heard the contraction of the ventricular muscle as seen on fluoroscopy is less incisive and the cardiac shadow is increased as measured in the teleoroentgenogram

In the heart in which there is a *right ventricular preponderance* (p 869) the accentuated second sound becomes less marked the jugular veins appear more prominent there is greater filling of the retrocardiac space the right auricle bulges laterally

Backward Failure —When the capacity of the cardiac reserve has been exceeded the patient progresses to the stages of backward failure with

dose to detect sensitization capsules containing 0 3 gm (5 grains) are given every three hours and the amounts are gradually increased up to 1 5 gm (22 grains) five times daily if the irregularity persists at the expense of circulatory efficiency

In a rare emergency when the patient is moribund an attempt may be made to terminate the ventricular tachycardia by a slow intravenous injection of *quinine sulfate* (p 517) This measure of heroic therapy is not without danger and may result in sudden death due to asystole *Digitalis* is usually contraindicated

VENTRICULAR FIBRILLATION

Ventricular fibrillation is the most serious of the cardiac irregularities It is characterized by a rapid totally irregular arrhythmia of a bizarre character The electrocardiographic tracing is difficult of interpretation since P Q R and S waves become fused and indistinguishable The condition is rapidly fatal and has usually terminated by the time of the arrival of the physician **(ECG 68)**

Ventricular fibrillation is very occasionally the cause of sudden death in instances *of coronary thrombosis* it also occurs in fatalities due to chloroform and electrocution If it is recognized at all treatment is best limited to the administration of an opiate since there is no method of determining whether digitalis or quinidine might prove helpful or harmful

CARDIAC TAMPONADE

The syndrome of *cardiac compression* may occur under acute or chronic circumstances The importance of its recognition rests in the fact that the condition may be alleviated by mechanical or surgical intervention

ACUTE CARDIAC TAMPONADE

Acute cardiac compression may accompany any condition in which there is an effusion of a fluid substance into the pericardial cavity Thus it is observed in *acute serous pericarditis* (p 1008) in *hemopericardium* particularly that which accompanies non penetrating injuries to the chest wall (p 2046) with *penetrating chest wounds* (p 968) and laceration of the heart or a coronary artery with rupture of a *myocardial infarct* or an *aortic aneurysm*

Clinical Manifestations—Acute cardiac tamponade is characterized by progressive weakness of the *pulse* faintness of the *heart sounds* a falling *arterial blood pressure* a rising *venous pressure* pallor coldness and clamminess of the skin progressive *dyspnea* and progressive increase in the area of *cardiac dullness* Electrocardiographic changes often pathognomonic include R T elevations T wave inversions and flattening of the QRS complexes (**ECG 16, 17, 46**)

Treatment—If acute cardiac tamponade is suspected the patient should be hospitalized *Pericardial aspiration* (p 852) is required a serous fluid may be evacuated in the presence of evidences of active bleeding surgical intervention by the expert is indicated in order to accomplish hemostasis which may prove life saving

CHRONIC CARDIAC TAMPONADE

Chronic cardiac compression is observed in instances of *concretio cordis* particularly with calcification and in *scleroderma* (p 3427) when the chest wall is completely hidebound

Clinical Manifestations.—The manifestations of chronic compression differ somewhat from those of acute tamponade *arterial pressure* is low *cardiac sounds* are distant *venous pressure* is high the *superficial veins* are dilated and evidences of *back ward failure* are superimposed so that edema, hepatosplenomegaly and ascites are readily demonstrable

Treatment—The recognition of a chronic cardiac tamponade requires *surgical consultation* In the presence of a pericardial lesion operative interference is within the realm of possibility The surgical approach to sclerodermatous compression is less clear but may be attempted by disarticulation of the costochondral junctions

dose to detect sensitization capsules containing 0 3 gm (5 grains) are given every three hours and the amounts are gradually increased up to 1.5 gm (22 grains) five times daily if the irregularity persists at the expense of circulatory efficiency

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(p 1342) in origin These disturbances have the most optimistic prognosis and respond best to therapy

Autonomic Arrhythmias—Disturbances of autonomic innervation lead to many of the arrhythmias pressure on the carotid sinus results in sinus bradycardia or cardiac standstill with syncope (p 921) *vasovagal disturbances* occur from *anatomic lesions* (acute myocardial infarction) from *reflex stimulation* of trigger points (the eye the point of the jaw the solar plexus the testicle the pleural and peritoneal membranes) and from *pharmacological effects* with cholinergins vagal inhibitor, adrenergic preparations or digitalis

Metabolic Arrhythmias—*Irregularities occasionally result from metabolic disturbances* *hyperthyroidism* (p 1197) produces sinus tachycardia ventricular premature contractions and auricular fibrillation the effect of *tobacco* (p 3884) and *caffeine* (p 3860) *warrants scrutiny in the investigation of irregularities of otherwise unknown etiology*

Arrhythmias of Organic Origin—The more serious and persistent irregularities are almost all due to organic disease At least half of the cardiac invalids whether incapacitated by *rheumatic fever* (p 186) or *teriosclerosis* (p 976) or *congenital defects* (p 956) suffer from cardiac irregularities usually auricular fibrillation

SINUS TACHYCARDIA

With sinus tachycardia the cardiac rate exceeds 100 beats to the minute the electrocardiographic picture of the individual cycle reveals no consistent significant abnormality (ECG 5, 21, 24, 28, 50)

Pathogenesis —Sinus tachycardia is due to a dominance of the normal accelerator mechanism it is one of the many manifestations of *autonomic imbalance* and may have no pathologic connotation (p 1395)

Etiology —Sinus tachycardia may be *permanent* under which circumstance it represents an autonomic imbalance most often seen in childhood and adolescence It may be *transitory* resulting from pharmacologic physiologic or pathologic causation Thus it appears in those receiving atropine and similar vagal depressants after adrenergic drugs particularly amphetamine sulfate (benzedrine) with overdosage with thyroid extract from excessive doses of cocaine and after a bout of alcoholism

A rapid heart rate follows eating exercise and emotional stress it is *observed in normal persons at high altitudes* The pathologic causes of tachycardia include *hyperthyroidism* (p 1197) *anemia* (p 1055) and most *infections* except typhoid fever it is noted also in *backward failure* (p 941) and in *hemorrhage* (p 1057)

Clinical Manifestations —Persistent sinus tachycardia is asymptomatic unless an *anxiety state* (p 1347) is created by a timorous examiner The pathologic varieties are often accompanied by *palpitation* and extreme instances are capable of producing *angina pectoris* (p 890) or a *coronary insufficiency* (p 895)

Diagnosis.—The diagnosis of the cause of sinus tachycardia is established by the method of *exclusion* The practitioner must ascertain the fact that the condition is not symptomatic of a *febrile disorder* particularly incipient tuberculosis (p 258) hyperthyroidism (p 1197) or a smoldering rheumatic fever (p 189) Before committing himself to an opinion

in those addicted to the use of tobacco and in uncontrolled diabetes associated with hypercholesteremia and obesity

Precipitating Causes—The attack of angina is usually precipitated by some definite provocative influence It may follow exertional or emotional excitement a brisk walk climbing stairs walking uphill exposure to cold a heavy meal straining at stool sexual intercourse or some combination of these activities such as walking after a heavy meal

The Attack—The individual attack of angina pectoris may vary in location character and intensity Most often the episode comes on acutely the pain is definitely *substernal* or *precordial* and is often described as a sense of constriction The *intensity* of the distress may be slight or so great as to give a sense of impending dissolution *Relief* may be experienced with the same rapidity as the speed of onset following the attack neither the patient nor his electrocardiographic tracing appears any the worse for the experience

The anginal pain may differ in its *location* in different individuals it may be retrosternal epigastric referable to the left shoulder shoulder blade or arm it may be interscapular

The *radiation* of the pain is a variable it may remain quite localized it may radiate to the left shoulder and down the inner or outer surface of the left arm into the fourth and fifth fingers it may spread to the neck and jaw it may advance to both shoulders and both arms

Many different characteristics of the sensation are reported by various individuals some report a mere sense of compression in others the attack is agonizing still others describe the pain as lancinating stabbing knife like squeezing or constricting *Hyposensitive individuals may* report merely that they have some type of paresthesia such as a tingling or *burning sensation*

Associated Phenomena—While the angina is the dominant manifestation of the disturbance the patient may also present associated phenomena These include the presence of cold perspiration clamminess dizziness weakness palpitation dyspnea inability to breathe intense anxiety and the sense that death is imminent

Duration and Recurrences of Attacks—Angina pectoris may be an almost transitory affliction in other instances a *status anginosus* develops with persistence of the pain until its victim is rendered almost unconscious by the cumulative effect of the sedative drugs

Anginal attacks are rarely isolated most often they occur with regularity upon repeated provocation The patient learns the limit of what he can accomplish with relative comfort he develops anxiety and tension as soon as he approaches the known boundary of his tolerance and this fact often precipitates an attack prematurely

Pharmacological Tests—The diagnosis of angina pectoris may be confirmed by pharmacological tests relief of symptoms should be afforded by the use of *nitroglycerin* (p 3892) or inhalations of oxygen (p 3828) Under institutional conditions the practitioner may precipitate an attack by *exercise* or the production of *anoxemia* through rebreathing in an anesthesia bag or a spirometer Neither of the provocative procedures should be carried out unless the physician is in attendance and prepared to offer relief by the administration of nitroglycerin or oxygen *Objective evidence*

Treatment —The treatment of sinus tachycardia requires only the physician s reassurance to the patient Normal activity and exercise are encouraged rather than interdicted *Children* and adolescents should not be warned that they have weak hearts nor forbidden to indulge in athletic competition

The patient with sinus tachycardia is not to be digitalized unless there are evidences of heart failure The administration of this drug does not slow the rate but will seriously interfere with cardiac efficiency (p 951) it has no potentiality for benefit and engenders considerable risk from pharmacologic and psychologic aspects

SINUS BRADYCARDIA

Sinus bradycardia represents the converse of sinus tachycardia (p 874) there is excessive *slowing* of the pulse rate but no significant consistent alteration in the electrocardiogram **(ECG 51)**

Pathogenesis —*In sinus* bradycardia the vagus mechanism is dominant and there is slowing of impulse production The phenomenon is another manifestation of *autonomic imbalance* and is often observed in those who are *said to suffer from vagotonia* in which there are associated spasmodic disturbances *in the* gastro intestinal tract (See p 1395)

Etiology —Sinus bradycardia is seen physiologically in sleep (p 1804) and *in athletes* in training Symptomatic bradycardia occurs as the result of *myxedema* (p 1193) *in the cholemia* of obstructive jaundice (p 1953) from *overdigitalization* and with *increased intracranial tension* (p 1421) Under any of these conditions the minute rate may be as slow as 35 to 40

Clinical Manifestations —Physiologic bradycardia is asymptomatic The *pathological* variations particularly those induced by digitalis in the damaged heart may cause evidences of *backward failure angina* or *coronary insufficiency*

Diagnosis —*Sinus* bradycardia requires differentiation from *heart block* (p 879) for complete assurance the practitioner is safeguarded by obtaining an electrocardiogram (p 802) An estimation of the basal metabolic rate (p 3738) is advisable if there is any suspicion of a *hypothyroidism* (p 1191)

Treatment —There is a great temptation to treat sinus bradycardia with the vagal depressants such as atropine and belladonna These drugs accomplish nothing of value to the patient and may cause considerable distress due to dryness of the mouth or dilatation of the pupil As in the instance of sinus tachycardia alarmists may precipitate the patient into an *anxiety neurosis* (p 1347) by intimations that the heart is weak by rejection in insurance examination or by raising premium payments There is no physiologic or clinical justification for these practices

Those patients whose bradycardia is accompanied by a lowering of the basal metabolic rate are given probatory doses of *thyroid extract* (p 1189) in order to determine whether the correction of the laboratory phenomenon is associated with a greater sense of well being If the patient feels more fit while under the influence of the drug its administration is continued in maintenance dosage (p 1190) otherwise the use of the extract is abandoned

of the angina is provided by taking *serial electrocardiograms* and demonstrating transitory alterations in the ST and T waves (p 711) during the periods of anoxemia or after exercise (p 818)

Physical Examination During the Attack —There are no characteristic physical findings during the attack of angina pectoris The intensity of the pain causes the pulse rate to rise and the blood pressure to become somewhat elevated At times it may be possible to demonstrate a band of *cutaneous hyperalgesia* but the objective phenomena are inconsequential in comparison to the intensity of the subjective distress

The Electrocardiogram —The electrocardiographic tracing taken during or following an attack of angina pectoris usually shows no consistent abnormality unless a coronary insufficiency has been produced (ECG 11 12, 13, 14, 61) These changes may be reproduced for diagnostic purposes by the *two step test* (p 789)

Complications —The syndrome of angina pectoris is a harbinger of increasing circulatory difficulty While the exceptional individual may learn to live within his limitations and pursue a relatively uncomplicated course for many years more often the anginal seizure is followed by increasing circulatory difficulties or interpolated episodes of *acute coronary occlusion* (p 983) and *myocardial infarction* (p 992)

Treatment —The primary aim of the practitioner in the management of an angina pectoris is to attack the problem at its root and eliminate those factors which are adding to the circulatory burden The details of the therapeutic campaign are elaborated with the discussion of the measures employed in dealing with the patient who suffers from circulatory deficiency (p 920) Symptomatic therapy aims at the immediate control of the acute attack and measures directed at the prevention of further difficulty

The Acute Attack —The sovereign remedy for the relief of the acute attack of angina pectoris is *nitroglycerin* (p 3893) The patient must be equipped with a quantity of tablets of 0 65 to 0 3 mg (1/100 to 1/200 grain) At the onset of the seizure or a suggestion of its impending presence the victim sits or preferably lies down and places a tablet under the tongue Within a few seconds the onset of the pharmacologic effect is evidenced by flushing of the face palpitation a pounding in the head and a blessed relief to the anguish Obstinate attacks may require repetition of the dose two or three times at five to ten minute intervals

Some patients prefer to inhale the fumes of *amyl nitrite* This preparation is packaged in frangible ampoules which can be broken in a handkerchief and inhaled for a very rapid effect side effects are more apt to be unpleasant however and the tablets of nitroglycerin are preferred

In the absence of nitroglycerin or amyl nitrite a drink of *whiskey* or *brandy* which may be more readily available frequently alleviates anginal pain For obvious reasons nitroglycerin is preferred if available

The optimum physiological method of relieving angina pectoris is by the inhalation of *oxygen* (p 3827) If it is at all practicable those who are subject to anginal seizures are advised to purchase an oxygen tank with its necessary valves and gauges and some type of easily adjustable mask similar to that used in aviation At the suggestion or onset of difficulty

cardiographic changes which are characterized by alterations in the shapes of the P waves As the pacemaker moves toward the auriculoventricular node the P wave may follow, precede or occur simultaneously with the QRS complex (ECG 56, 57)

The wandering pacemaker unless accompanied by other manifestations of circulatory disease requires no particular therapy

AURICULOVENTRICULAR NODAL PREMATURE CONTRACTIONS

See *Premature Contractions* (p 887)

AURICULOVENTRICULAR NODAL RHYTHM

The rare abnormality of AV nodal rhythm is characterized by the initiation of the impulse at the junctional tissue rather than in the region of the normal pacemaker The impulse spreads simultaneously to auricles and ventricles the normal P wave usually follows or distorts the QRS complex the resultant cardiac rate ranges between 30 and 50, approaching the idioventricular count

The etiology of auriculoventricular nodal rhythm is unknown though it may be caused by excessive doses of or sensitization to *digitalis* (p 860) If the drug is being administered its continued use is hazardous The patient who is not exposed to the drug and has no circulatory manifestations requires no particular therapy

AURICULOVENTRICULAR NODAL PAROXYSMAL TACHYCARDIA

See *Paroxysmal Auricular Tachycardia* (p 881)

SINUS ARREST

On rare occasions the sinus node fails to initiate one or more beats When a single impulse is dropped there are rarely any manifestations and the condition is noted in the course of electrocardiography The failure of several beats to start at the sinus may result in *syncope* similar to that noted in patients with hypersensitive carotid bodies (p 922) Sino-auricular block or arrest may be due to the effects of *digitalis* (p 854) *quinidine* (p 861) or *potassium salts* (p 601)

With marked depression of the sino auricular node an *ectopic focus* may serve as an interim pacemaker Under these circumstances the electrocardiogram shows normal complexes with interspersed abnormal cycles the periods of asystole measure exactly the length of one or more cycles (ECG 53)

Treatment —The management of sinus arrest follows the principles elsewhere discussed with relation to the hypersensitive carotid bodies (p 922) A trigger mechanism may be discovered such as turning of the head the wearing of a tight collar gagging or any motions that produce pressure on the sensitive zone The use of 16 mg phenobarbital (¼ gr) and 2? mg ephedrine (⅓ gr) in capsule form is advocated paredrine 40 to 60 mg (⅔ to 1 grain) may be given orally three times daily physiological doses of atropine may be tried separately or simultaneously In extreme instances, denervation of the carotid may merit consideration

lative poisoning If no improvement is noted the use of the drug is abandoned but repeated efforts are made every few months

24 A course of 6 to 10 intramuscular injections of androgen 10 to 25 mg given at two or three day intervals repetition of the course following an intermission of a week to ten days if the patient s reported improvement justifies the expense (p 2404)

25 The use of an injection of a mercurial diuretic and the oral ad ministration of ammonium chloride in those who have evidences of edema or of backward failure (p 941)

Nerve Block—In intractable angina pectoris symptomatic relief may be afforded by nerve block (p 853) Alcohol is injected into the upper thoracic areas to produce a paravertebral block this procedure has sup planted surgical extirpation of the ganglia

Paravertebral injections of alcohol produce splendid results in approx imately two out of three individuals provided that the technical consid erations are accurately followed Relief of pain is usually permanent in the more successful instances in the less fortunate the attacks persist but with lessened intensity In the most unfortunate patient a painful intercostal neuritis is substituted for the angina and may prove more harassing to the victim than his previous distress

Paravertebral alcohol injections require the services of the expert since accidents may be encountered the latter include the production of a pleural effusion or a pneumothorax local hemorrhage from a perforated artery a transverse myelitis or sudden death from direct injection of the alcohol into the blood stream

ACUTE CORONARY INSUFFICIENCY

An acute coronary insufficiency exists when there is a disproportion between the oxygen requirements of the myocardium and the coronary blood flow Attacks may be provoked by factors which increase the work of the heart reduce the coronary circulation or decrease the oxygen carrying capacity of the blood

Etiology—The more tangible etiologic causes for acute coronary in sufficiency include those factors which interfere with coronary circulation and those which increase the necessity for an augmented volume output Attacks are precipitated by acute hemorrhage postoperative shock pul monary embolism attacks of paroxysmal cardiac irregularity sudden strains in patients with mitral or aortic stenosis and insufficiency and excruciating pain such as occurs in acute pancreatitis or agonizing injuries

Pathology—An acute coronary insufficiency of mild degree and short duration does not cause demonstrable changes in the myocardium More intense or protracted examples however result in the production of dis seminated foci of myomalacia The involved areas are largely subendo cardial and involve particularly the papillary muscles and the interven tricular septum These manifestations of myocardial infarction are not ac companied by coronary occlusion and may occur in the absence of sig nificant amounts of coronary sclerosis

diopathies due to diphtheria (p 302) and syphilis (p 331) on rare occasions it may be congenital

Clinical Manifestations—Complete heart block may exist in patients who have no evidences of any related clinical manifestations Sooner or later however it is likely that episodes of cerebral anoxemia will be encountered with the associated development of the Stokes Adams syndrome Under the latter circumstance transitory ventricular standstill is associated with only slight *vertigo* The continuance of the period of asystole for more than 30 seconds usually results in *loss of consciousness* with *convulsions* and unless this condition can be controlled a fatal episode ensues

Diagnosis—The diagnosis of complete heart block requires electrocardiographic study The complete absence of any relationship between auricular and ventricular complexes leaves little doubt as to the nature of the derangement (**ECG 77, 78, 79, 80**)

Treatment—The patient with an asymptomatic heart block does not require treatment Those with a complete dissociation between auricles and ventricles and histories of episodes of vertigo or syncope should be *digitalized* under these circumstances the drug effect on conduction is not capable of any increased damage and the muscle effects may be beneficial Each course of treatment is regarded as an individual experiment patient and physician must collaborate in the attempt to evaluate the efficacy of the pharmacological agent If the course of digitalization seems beneficial its continued use is advised if the effects are questionable the drug is stopped and then resumed at the end of another week or ten days in order to obtain more definitive information

After the effects of the digitalis have been established similar probatory courses are advised using *atropine* and *aminophylline* alone or in combination Injections of *barium* advocated by expert and experienced cardiologists are much too dangerous for routine use in clinical practice

Attempts may be made to prevent the Stokes Adams attacks by the use of the sympathomimetic amines, 1 1000 epinephine hydrochloride or 1 per cent neosynephrin may be given by subcutaneous injection or intranasal spray *ephedrine sulfate* is administered orally in doses of 24 mg (3/8 grain) three times daily *amphetamine sulfate* (benzedrine) is administered in tablets of 5 to 10 mg (1/12 to 1/6 grain) *barium chloride* may be prescribed in doses of 32 to 45 mg (1/2 to 2/3 grain) three times daily in combination with the amines

TREATMENT OF THE ATTACK—In the presence of a syncopal attack heroic therapy is required The patient may be given subcutaneous injections of epinephrine hydrochloride (1 1000) or 1 per cent neosynephrine in doses of 0.5 to 1 cc a 1 100 solution of epinephrine may be sprayed intranasally as in the treatment of asthma (p 2095) paredrine 10 to 20 mg (1/6 to 1/3 grain) may be injected intramuscularly intracardiac injections of 0.5 to 1 cc of the 1 1000 epinephrine are attempted as measures of desperation a continuous intravenous drip of 1 100 000 epinephrine may be instituted

INTRAVENTRICULAR CONDUCTION DEFECT (BUNDLE BRANCH BLOCK ARBORIZATION BLOCK)

An intraventricular conduction defect or block may be due to involvement of the AV bundle its branches or the fibers of Purkinje The com

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NOTE Boldface indicates colored illustration

ular tachycardia usually responds to vagal stimulation such as pressure on the carotid sinus or the induction of emesis by ipecac (p 1757) *exercise* has no effect on the irregularity In *auricular fibrillation* (p 885), there is considerable increase of the rate following exercise but no effect is noted from carotid sinus pressure, the pulse is totally irregular, counts taken at different times vary considerably as opposed to the regularity of the auricular tachycardia With an *auricular flutter* (p 883), carotid sinus pressure produces temporary slowing but there is no change in the rate as the result of exercise a paroxysm of *ventricular tachycardia* is not affected by vagal stimulation or exercise and the rate is slightly irregular

Treatment—Paroxysms of auricular tachycardia can usually be terminated by *reflex vagal stimulation* Usually each patient finds an individual method that is most effective for his needs These technics include standing on the head doubling over the back of the chair to exert pressure on the splanchnic areas breath holding the insertion of a suppository or finger in the anal canal the use of an enema or the induction of emesis by digital stimulation of the pharynx

TABLE 54—DIFFERENTIAL DIAGNOSIS OF PAROXYSMAL TACHYCARDIA

	Vagal Stimulation	Exercise	Rate
Paroxysmal Auricular Tachycardia	Occasional return to normal	No effect	Absolutely regular
Paroxysmal Ventricular Tachycardia	No effect	No effect	Slight irregularity
Auricular Fibrillation	No effect	Increased rate	Rapid and irregular occasionally difficult to determine
Auricular Flutter	Temporary slowing	No effect	Slight irregularity

Vagal Stimulation—If the attack continues the patient is entitled to a dose of an opiate (2 mg dilaudid [1/32 gr]) to allay anxiety and distress Thereafter the physician notes the effects of pressure on the eyeballs or the carotid sinus With the patient in the recumbent position, the operator applies pressure for 5 to 10 seconds with one hand while with the other hand he holds the stethoscope at the apex so that vagal stimulation may be terminated as soon as the ear perceives a change in the cardiac mechanism If this precaution is not observed continued pressure may produce cardiac standstill with distressing results for both physician and patient

When reflex pressure is made over the eyeballs the finger and thumb of one hand are pressed sufficiently deeply into the sockets to cause considerable pain, carotid sinus pressure is tested first on the *left* and then on the right side it must be sufficiently heavy to obliterate the artery by rubbing against the spinous process

Emetics—While manual methods of vagal stimulation often afford a dramatic cessation of the irregularity it is far safer to use drugs that

the electrocardiograph revealing the characteristic flutter waves which occur between 200 and 300 to the minute (ECG 61, 62, 63)

See *Differential Diagnosis of Paroxysmal Tachycardia* (p 882)

Treatment —Paroxysmal auricular flutter is treated in the manner of a paroxysmal auricular tachycardia (p 882) Chief reliance is placed upon attempts to terminate the attack by reflex vagal stimulation sedation is administered liberally doses of quinidine are prescribed for active and prophylactic effects In most instances digitalization is required before the condition can be controlled

PERMANENT AURICULAR FLUTTER

Permanent auricular flutter resembles the paroxysmal attacks so far as electrocardiographic appearances are concerned and in the pathological physiology The arrhythmia is rarely seen except as a complication of organic heart disease when it is most often a chance finding in an electrocardiographic study (ECG 61, 62, 63) Of itself it has no particularly characteristic clinical manifestations except insofar as it contributes to circulatory deficiency

Treatment —The maneuvers employed for the termination of an episode of paroxysmal auricular flutter hold no promise in the management of the permanent variety Main reliance is placed upon the administration of *digitalis* and *quinidine* separately or together

Digitalis —Digitalization is attempted in each example of permanent auricular flutter and in those paroxysmal attacks that fail to respond to vagal stimulation A total dose of 1 5 to 1 75 gm (22½ to 27 grains) is given in the first twenty four hours using 0 8 gm (12 grains) as an initial dose 0.5 gm (7½ grains) four hours later 0 32 gm (5 grains) after another four hours and 0 2 gm (3 grains) as the last dose With effectual dosage a 4 to 1 or 6 to 1 block is established with slowing of the ventricular rate to the region of 70 to 80 beats to the minute When this amount of ventricular slowing has been accomplished a small percentage of the patients with flutter will progress to auricular fibrillation at this time the administration of digitalis is discontinued since experience has shown that normal rhythm may be reestablished at the end of another day or two

Quinidine —In the majority of patients who do not progress through the sequence of auricular fibrillation and resumption of sinus rhythm during digitalization doses of quinidine are substituted or supplemented Capsules containing 0 2 to 0 3 gm (3 to 5 grains) are administered at three-hour intervals following probatory doses given to detect sensitivity (p 861) If quinidine produces no untoward effect and the flutter continues increasing amounts are given until sinus rhythm is established or the zone of toxicology is entered With an effectual quinidine course the refractory periods of the auricular and ventricular muscle fibers are increased the circus movement is broken up the auricular rate is slowed but there is no direct effect on auriculoventricular conduction

Prophylaxis —Once an auricular flutter has been terminated a return of the irregularity may be prevented by continued digitalization or interval doses of quinidine Clinical experience may indicate the efficacy of digitalization alone or it may prove wiser to give quinidine for several days

the drug must be administered as in the instance of permanent auricular fibrillation (p 886)

PERMANENT AURICULAR FIBRILLATION

The electrocardiographic appearances and the pathologic physiology of permanent auricular fibrillation are identical with those of the paroxysmal variety (p 885)

Etiology—Permanent auricular fibrillation is most often associated with rheumatic or arteriosclerotic heart disease (p 976) it occurs also in hyperthyroidism (p 1197) particularly in the masked variety

Clinical Manifestations—Permanent auricular fibrillation does not produce any pathognomonic clinical manifestations The arrhythmia appreciably adds to circulatory inefficiency The unfavorable influence of auricular fibrillation is best illustrated by the presence of the irregularity in at least 50 per cent of cardiac invalids

Diagnosis—The diagnosis of permanent auricular fibrillation offers little difficulty the clinician is aware of the irregular irregularity of apex and radial beats There is usually a clearcut pulse deficit between apex and radial count the electrocardiographic tracing reveals no evidence of P waves (I CG 23, 61, 64, 65, 70, 71)

Treatment—The sovereign remedy for permanent auricular fibrillation is *digitalis* (p 854) It is in this condition that the therapeutic effects of the drug are best demonstrated and toxicologic phenomena are least frequently encountered The drug does not influence the cardiac irregularity it superimposes a heart block protecting the ventricle from the nagging and ineffectual auricular contractions apex and radial beats are reduced to the vicinity of 70 or 80 to the minute the pulse deficit is eradicated, there is marked subjective relief of dyspnea and precordial distress edema fluid is eliminated by a profuse diuresis best measured by loss in weight that may reach five to ten pounds, pulmonary hypostasis (p 2086) is ameliorated and peripheral edema is dissipated

Following the restoration of circulatory efficiency, a basal metabolic rate determination is warranted on slight suspicion of a possible *hyperthyroidism* (p 1197) If an elevation exists in the absence of circulatory deficiency a therapeutic test with *iodide* (p 1213) is indicated In the presence of a positive iodide response the advisability of *subtotal thyroidectomy* (p 1214) is taken under serious consideration

Whether or not the underlying cause for the fibrillation is a hyperthyroidism maintenance of circulatory efficiency must be sought after restoration of the cardiac breakdown Adequate doses of digitalis are given daily but with interruption to prevent cumulative poisoning (p 860) and efforts are made to reduce physical and mental activity to a level that is within the patient s potentiality If there is a suspicion that the attack may have been paroxysmal a course of *quinidine* may be instituted as soon as compensation has been reestablished However if sinus rhythm cannot be restored and maintained with comparative ease it is better to accept the presence of the fibrillation and maintain the patient under constant digitalization

IDIOVENTRICULAR RHYTHM

When the ventricle acts as its own pacemaker as it does in complete heart block (p 870) the rate is usually maintained between 15 and 50

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in the timing or the character of the premature heart sound an ineffectual beat is audible at the apex but not palpable in the radial artery ventricular premature contractions are followed by a compensatory pause that is longer than that between two normal beats the jugular vein may show a more pronounced bulge corresponding to the premature contraction when there is backward pressure in the auricles due to their simultaneous contraction with the ventricles

A final distinction between the types of premature contractions requires electrocardiographic tracings Premature contractions are generally abolished when the heart rate is increased beyond 100 by exercise this latter observation is in contrast to the conditions that prevail in auricular fibrillation in which induced tachycardia has no appreciable effect on the irregularity

Prognosis and Treatment—The presence of premature contractions has no serious implication unless they serve to make the patient heart conscious and precipitate or aggravate an anxiety neurosis (p 1347) It is the duty of the practitioner to acquaint the patient with his cardiac irregularity and assure him that it has no important connotations The presence of the arrhythmia must not keep the individual from carrying out normal activity and participation in sports or athletic competition

The management of premature contractions requires first that *exciting causes* be eliminated The use of alcohol coffee tea and unnecessary drugs such as headache remedies is forbidden smoking is interdicted and the use of digitalis is strictly avoided Positive therapy involves the use of *sedatives* in those who are apprehensive and of doses of *quinidine* (p 861) if the irregularities are frequent and particularly annoying *Exercise* is encouraged and the patient and his relatives are warned concerning the evils of coddling

In rare instances where the premature contractions persist despite the measures above mentioned an attempt at *digitalization* is worthy of consideration If the drug causes disappearance of the irregularity re examinations are conducted after cessation of the medication in order to determine whether maintenance doses are advisable

PAROXYSMAL VENTRICULAR TACHYCARDIA

Paroxysms of ventricular tachycardia usually produce regular rates between 160 and 200 beats to the minute higher rates may also be encountered

Etiology—Paroxysms of ventricular tachycardia generally accompany severe organic heart disease they may occur as the result of a coronary thrombosis or as a manifestation of overdigitalization

Clinical Manifestations—Episodes of paroxysmal ventricular tachycardia cannot be differentiated clinically from those that arise in the auricle (p 881) The decision as to the nature of the irregularity rests upon the appearance of the electrocardiogram and even this may not afford clearcut differentiation (ECG 66, 71)

Diagnosis—See *Differential Diagnosis of Paroxysmal Tachycardia* (p 882)

Treatment—Paroxysmal ventricular tachycardia is most satisfactorily treated by adequate doses of *quinidine* (p 861) After an initial probatory

CHAPTER 39

PHYSIOLOGICAL DISTURBANCES OF THE CIRCULATORY SYSTEM MYOCARDIAL ISCHEMIA ANGINA PECTORIS NEUROCIRCULATORY ASTHENIA

ACUTE MYOCARDIAL ISCHEMIA OR ANOXIA

The nutrition of the myocardium is essential for the efficient accomplishment of circulatory function An acute ischemia or anoxia may arise from distant or local causation The incident may be isolated or iterated it may be due to a deficiency in coronary flow a pathologic lesion of the musculature or a change in the quality of the circulating fluid

Acute myocardial ischemia may become manifest by the isolated symptom complex of *angina pectoris* or it may give rise to the more complex manifestation of *acute coronary insufficiency*

ANGINA PECTORIS

Angina pectoris is a symptomatic complaint it is not a specific clinical syndrome but it arises from myocardial anoxia or ischemia of whatever origin

Definition —The present concern is limited to those attacks of angina pectoris in which there is a presumed myocardial anoxia but not sufficient significant organic disease to present definitive electrocardiographic or other abnormalities

Etiology —In the vast majority of instances angina pectoris is due to *arteriosclerosis of the coronary arteries* (p 976) As a result of the impoverishment of the blood supply to the myocardium episodes of anoxia are encountered with the production of the characteristic attack Angina pectoris accompanies *acute coronary insufficiencies* next to be described it may also be a manifestation of the organic disturbances of the heart such as *coronary artery occlusion myocardial infarction or myomalacia*

Predisposing Factors —There is a definite predisposition to the development of angina pectoris The syndrome occurs predominantly in the *male* there is a definite *familial tendency* to the affliction it occurs most frequently in the fourth, fifth and sixth decades

It is encountered disproportionately in those who have manifestations of cerebral or peripheral vascular arteriosclerosis, in hypertensives in hyperthyroidism, in polycythemia vera, in thromboangiitis obliterans

DIFFERENTIAL DIAGNOSIS OF

Precordial Pain

Precordial pain requires meticulous investigation since it is associated with grave insecurity with reference to the circulatory apparatus If acute persistent or recurring the practitioner should insist upon a chest x ray and serial electrocardiograms

	DIAGNOSTIC FEATURES
Cutaneous	Herpes zoster with band of hyperalgesia before appearance of eruption (p 435)
Mammary	From trauma due to ill fitting brassieres. With congestion due to pendulous or caked breasts and premenstrual tension. With lactation or breast abscess (p 2612) in chronic cystic mastitis (p 2580)
Muscular	Toxic as in influenza With myogelosis and myositis (p 2894)
Skeletal	Particularly with subluxation of costochondral junctions. With localized rib fracture or dislocation With bone neoplasm or osteomyelitis Get x rays
Pleural	With acute fibrinous pleurisy epidemic pleurodynia pneumothorax and empyema thoracis Note friction rub Confirm physical signs with chest x ray
Bronchopulmonary	*With localized lobar pneumonia, acute or* chronic pneumonitis lung abscess or neoplasm Get sputum temperature record and chest x rays.
Vascular	
Angina Pectoris	Acute episodes usually exertional Relieved by rest and nitroglycerin Normal Ecg temperature curve and blood count (p 890)
Coronary Insufficiency	Usually exertional with transitory cardiographic changes and normal temperature curve and blood count (p 895)
Coronary Occlusion	Not necessarily exertional with definite and progressive cardiographic changes fever leukocytosis and increased sedimentation rate (p 983)
Acute Pericarditis	With *to and fro friction* rub (p 1007)
Neurocirculatory	With intense anxiety but normal cardiovascular status (p 897)
Paroxysmal Cardiac Irregularity	Probably due to coronary insufficiency Get Ecg (p 882)
Aortitis	With dilatation or aneurysm Get x rays in several positions Wassermann test and Ecg (p 1025)
Alimentary	From esophagospasm, diaphragmatic hernia peptic esophagitis gastrospasm or trapping of gas in fundus or splenic flexure (stitch in side) Get barium x ray Consider esophagoscopy (p 1720)

the mask is adjusted oxygen flow is started and a high tension is inhaled until evidences of distress have been dissipated

Prophylaxis—Immediately following the relief of an anginal seizure the physician initiates his campaign against recurrence of the affliction In accordance with the principles established for the management of backward failure the following topics are considered

1 An alteration in the way of life (p 3474)
2 Weight reduction by diet (p 669)
3 Weight reduction by diet and the use of thyroid extract in those who have a low basal metabolic rate (p 1189)
4 Prevention of infection (p 947)
5 Control of hyperthyroidism by the use of iodide (p 1213) deracil (p 1150) and subsequent subtotal thyroidectomy (p 2214)
6 Control of polycythemia vera by repeated phlebotomies (p 1092)
7 Measures aimed at the control of hypertension (p 911)
8 Measures aimed at the control of a diabetes (p 1252)
9 Psychotherapy (p 1316)
10 Climatotherapy and spa therapy (p 3761)
11 Limitation of physical activity
12 Indulgence in sufficient physical activity to maintain muscle tonus without producing an anginal seizure (p 890)
13 'A rest cure' (p 3754)
14 Discontinuance of the use of tobacco
15 The daily use of sedatives such as phenobarbital 16 mg (¼ gr) after each meal
16 The nightly use of a hypnotic such as sodium seconal 0 1 gm (1½ gr) with a warm drink at bedtime
17 The substitution of frequent small meals for the usual three daily repasts
18 Prophylactic doses of nitroglycerin when the necessity for some unusual strain arises
19 The prophylactic use of whiskey or brandy at the end of the day or at bedtime as a nightcap
20 The prophylactic use of inhalations of oxygen where practicable when confronted with some unusual exigency
21 A period of ten days of trial with oral doses of a xanthine preferably aminophylline in tablets of 0 1 to 0 2 gm (1½ to 3 grains) three or four times daily Our experiences with this drug have not been encouraging though an occasional patient reports apparent relief from distress Under these circumstances the drug may be continued otherwise its use should be abandoned
22 A probatory period of ten days of iodide administration With improvement attempt functional thyroidectomy with propyl thiouracil (p 1212) observing extreme caution to avoid toxic manifestations
23 A probatory ten-day period of digitalization with repeated observation for reassurance that a toxic effect is not produced With reported improvement the drug may be given five days weekly with a two day rest period for the prevention of cumu